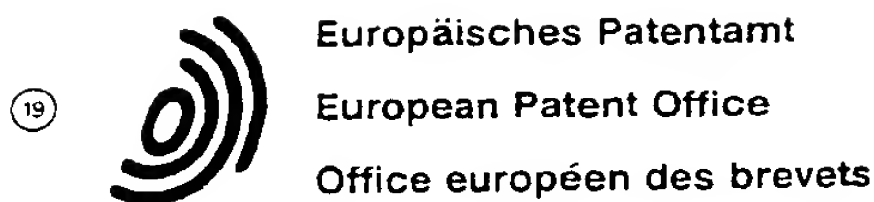


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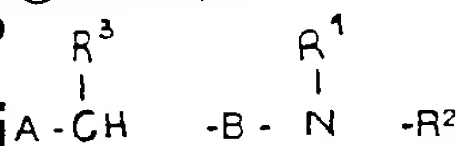
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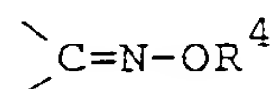
Aminoazole derivatives and their production and use.

A compound of the formula:



wherein A is the group of the formula:
 Ar¹ -D - Ar² -

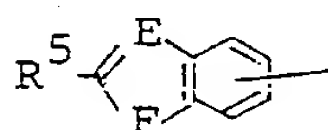
wherein Ar¹ is a phenyl or thienyl group which may be optionally substituted with at least one of the same or different halogen atom; Ar² is a phenylene or thienylene group which may be optionally substituted with at least one of the same or different halogen atom; D is a divalent radical selected from the group consisting of



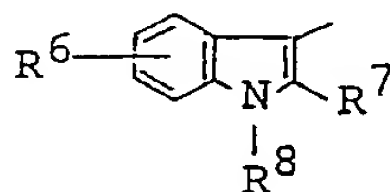
[wherein R⁴ is a hydrogen atom or lower alkyl group],



radical, or single bond,



wherein R⁵ is a lower alkoxy or a phenyl group which may be optionally substituted with at least one of the same or different halogen atom; E is a methine group or a nitrogen atom; F is a vinylene group or an oxygen atom,



wherein R⁶ is a lower alkoxy group; R⁷ is a lower alkyl group; R⁸ is a benzoyl group which may be optionally substituted with at least one of the same or different halogen atom,

B is a divalent azole group;

R¹ is a hydrogen atom or a lower alkyl group;

R² is a hydrogen atom, lower alkyl, aryl-lower alkyl, or the group of the formula:

R⁹ - G -

wherein R⁹ is a hydrogen atom, lower alkyl, halo-lower alkyl, amino-lower alkyl, aryl or aryl-lower alkyl group or the group of the formula:



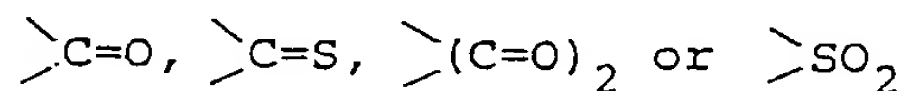
R¹⁰ - N -

wherein R¹⁰ is a hydrogen atom or lower alkyl group; R¹¹ is a hydrogen atom, lower alkyl, lower alkenyl, lower cycloalkyl, aryl-lower alkyl, aryl or aroyl group; or the group of the formula: -NR¹⁰R¹¹ is a 5-, 6-or 7-membered saturated heterocyclic ring; or the group of the formula:

R¹² - O -

wherein R¹² is a lower alkyl or polyhalo-lower alkyl group;

G is a divalent group selected from the group consisting of

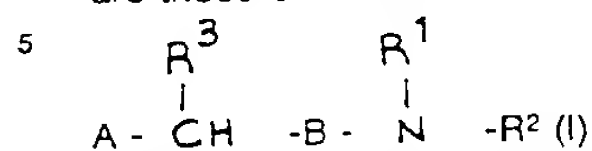


radical; or the group of the formula: -NR¹R² is a 5-, 6-or 7-membered saturated heterocyclic ring:

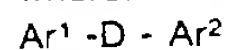
R³ is a hydrogen atom or lower alkyl group, or its acid addition salts, which is useful for immunomodulator.

AMINOAZOLE DERIVATIVES AND THEIR PRODUCTION AND USE

This invention relates to novel aminoazole derivatives useful as therapeutic and preventive agents of autoimmune diseases, for example, rheumatoid arthritis or systemic lupus erythematoses, inflammations, allergies and asthma, and their production and use. More particularly, the novel compounds of this invention are those of the formula:



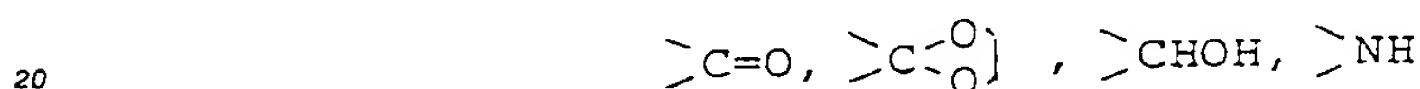
wherein A is a group of the formula:



- wherein Ar¹ is a phenyl or thienyl group which may be optionally substituted with at least one halogen atom;
Ar² is a phenylene or thienylene group which may be optionally substituted with at least one halogen atom;
D is a divalent radical selected from the group consisting of



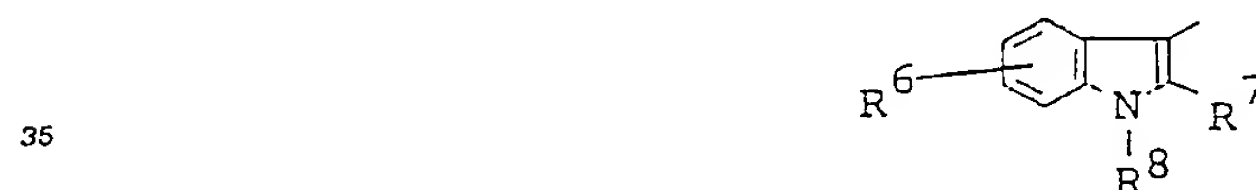
[wherein R⁴ is a hydrogen atom or a lower alkyl group],



radical, or a single bond; a group of the formula



- wherein R⁵ is a lower alkoxy or a phenyl group which may be optionally substituted with at least one halogen atom; E is a methine group or a nitrogen atom; F is a vinylene group or an oxygen atom; or a group of the formula

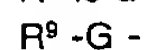


- wherein R⁶ is a lower alkoxy group; R⁷ is a lower alkyl group; R⁸ is a benzoyl group which may be optionally substituted with at least one halogen atom;

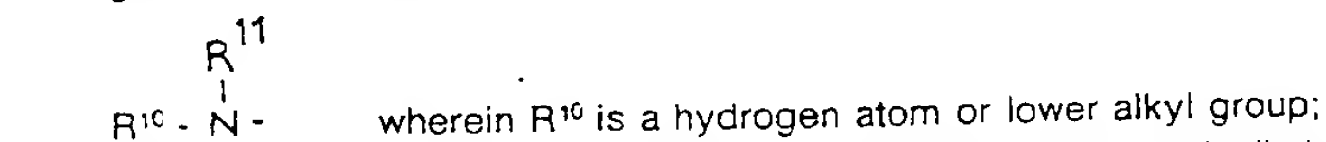
B is a divalent azole group;

R¹ is a hydrogen atom or a lower alkyl group;

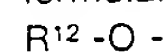
R² is a hydrogen atom, lower alkyl, aryl-lower alkyl, or the group of the formula:



- wherein R⁹ is a hydrogen atom, lower alkyl, halo-lower alkyl, amino-lower alkyl, aryl or aryl-lower alkyl group; or the group of the formula:

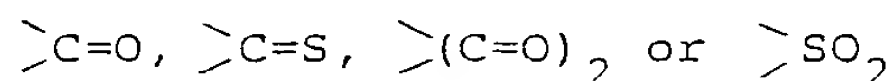


- wherein R¹⁰ is a hydrogen atom or lower alkyl group;
R¹¹ is a hydrogen atom, lower alkyl, lower alkenyl, lower cycloalkyl, aryl-lower alkyl, aryl or aroyl group; the group of the formula: -NR¹⁰R¹¹ is a 5-, 6-, 7-membered saturated heterocyclic ring; or the group of the formula:



wherein R¹² is a lower alkyl or polyhalo-lower alkyl group;

G is a divalent group selected from the group consisting of



radical; or the group of the formula: $-NR^1R^2$ is a 5-, 6-or 7-membered saturated heterocyclic ring;
 5 and R^3 is a hydrogen atom or lower alkyl group, and the pharmaceutically acceptable acid addition salts thereof.

Various compounds, such as steroids, non-steroidal anti-inflammatory drugs and gold compounds, are now widely used in the treatment of autoimmune diseases, for example, rheumatoid arthritis, but all of these drugs are of limited clinical use because of their side effects and unreliable clinical effects. As a result of
 10 the elucidation of the pathogenesis of autoimmune diseases, immunomodulators, which may alter the course of the diseases, have been used for the treatment of the diseases. As the immunomodulators, levamisole and D-penicillamine are described in the publications, Saishin Igaku, 35, 1392 (1980) and Igaku no Ayumi, 101, 216 (1977) respectively. However, they produce serious side effects, which cause a great problem in their clinical use.

15 It has been reported that aminoazoles have several biological activities. In recent years, 2-aminothiazoles such as fanetizole, 2-phenethylamino-4-phenylthiazole, (U.S. Pat. No. 4,307,106) and lotifazole, 4-phenyl-2-(2',2', 2'-trichloroethoxycarboxamido)thiazole, (E.P. Pat. No. 1,727), which regulate immune responses, have been reported.

In addition, 2-aminothiazole derivatives were described as gastric secretion inhibitor (E.P. Pat. No. 20 177,463). It was reported that 2-aminooxazole derivatives were effective against asthma (D.E. Pat. No. 2,459,380). It was reported that 5-aminoisoxazole derivatives were effective in cases of convulsions and acute inflammations (F. R. Pat. No. 2,068,418). 3-Amino-1,2,4-oxadiazole derivatives were described to be hypotensive drugs (F.R. Pat. No. 2,439,192), and carrageenin-edema inhibitors (D.E. Pat. No. 2,124,907).

Therapeutic agents for rheumatoid arthritis were also expected to be effective in the treatment of
 25 chronic inflammations and as regulants of the immune response in the body. The rat-adjuvant arthritis test is useful as pharmacological model to examine effects on chronic inflammations, and mice-Arthus reaction is useful as pharmacological model to examine the immune regulant activity.

D-penicillamine is not effective in the adjuvant arthritis test, and arthus reaction. Moreover, it has many severe side-effects. Levamisole is effective in the Arthus reaction, but is not effective in the adjuvant arthritis
 30 test and has many severe side-effects. Fanetizole and lotifazole are effective in the Arthus reaction, but are not effective in the adjuvant arthritis test.

Accordingly, the therapeutic agent for treating rheumatoid arthritis should contain a compound which is effective both in the adjuvant arthritis test and Arthus reaction, and should have less side effect.

As the result of an extensive study, it has now been found that the aminoazole derivatives (I) of the
 35 invention exhibit depressive activities in both the adjuvant arthritis and Arthus reaction, in addition to inhibitory activity for 5-lipoxygenase. Therefore, the aminoazoles (I) are useful for treating autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematoses inflammatory, allergy, asthma e.t.c. This invention is based on the above finding.

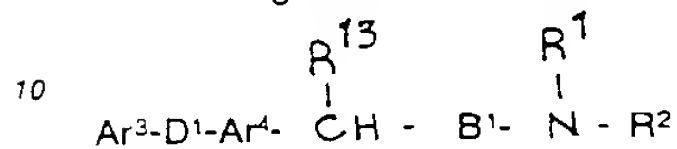
Accordingly, a main object of the invention is to provide the aminoazoles (I) and their pharmaceutically
 40 acceptable acid addition salts. Another object of this invention is to provide processes for producing the aminoazoles (I). A further object of the invention is to provide the aminoazoles (I) for use as immunomodulators or anti-inflammatory drugs.

In the compounds of the above formula (I) and elsewhere in the specification, the terms "alkyl" and
 45 "alkenyl" mean both straight and branched- C_{1-4} hydrocarbon chains, and the lower alkyl may be C_{1-4} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl. The lower alkenyl may be C_{2-4} alkenyl such as vinyl, allyl, n-propenyl, isopropenyl, 2-methyl-1-propenyl, 1-or 2-or 3-butenyl and the like. The lower alkoxy may be C_{1-4} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like. The halo-lower alkyl may be halo(C_{1-4})alkyl such as chloromethyl, bromomethyl, 1-chloroethyl, 2-
 50 chloroethyl, 1-bromoethyl, 2-bromoethyl, 1-chloropropyl, 2-chloropropyl, 3-chloropropyl and the like. The polyhalo-lower alkyl may be polyhalo(C_{1-4})alkyl such as trifluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl and the like. The amino-lower alkyl may be amino(C_{1-4})alkyl such as aminomethyl, 2-aminoethyl, 3-aminopropyl, 2-(N-methylamino)ethyl, 2-(N,N-dimethylamino)ethyl. The lower cycloalkyl may be a C_{3-6} alicyclic group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The aryl may be a phenyl group which may be optionally substituted with the lower alkyl group, such as phenyl, 4-
 55 methylphenyl, 4-ethylphenyl and 4-isopropylphenyl and the like. The aryl-lower alkyl may be phenyl(C_{1-4})alkyl such as benzyl, phenethyl, phenylpropyl. The substituted benzoyl may be a benzoyl group substituted with at least one halogen atom, e.g. 4-chlorobenzoyl, 4-fluorobenzoyl, 2-chlorobenzoyl, 2-fluorobenzoyl. The aroyl may be benzoyl or a benzoyl group substituted with at least one halogen atom, or at least one lower

alkyl group, which may be the same or different, e.g. 4-chlorobenzoyl, 4-fluorobenzoyl, 4-methylbenzoyl. The term "halogen" includes fluorine, chlorine, bromine and iodine. If the term "at least one halogen atom" stands for more than one halogen atoms, the halogen atoms may be the same or different. The 5-, 6-, 7-membered saturated heterocyclic ring may, for example, be pyrrolidinyl, piperidinyl, hexahydroazepinyl. The

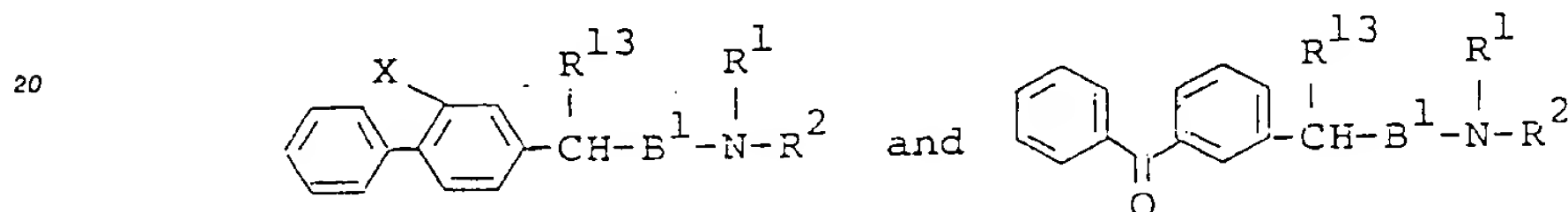
azole group is a 5-membered heterocyclic ring having one nitrogen atom and further at least one atom selected from the group consisting of oxygen, sulfur and nitrogen atom, such as, thiazole, oxazole, isoxazole, oxadiazole, isothiazole, thiadiazole, pyrazole, imidazole, triazole and the like.

Among the amino azole compounds (I) of the invention, those of the following formula are preferred:



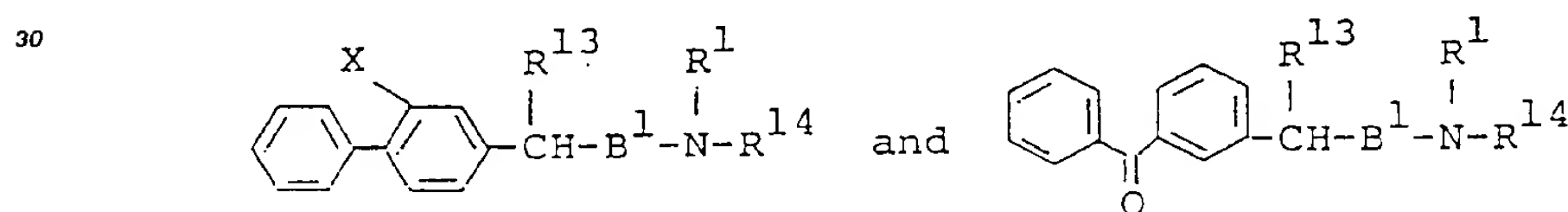
wherein Ar³ is a phenyl group which may be optionally substituted with at least one halogen atom; Ar⁴ is a phenylene group which may be optionally substituted with at least one halogen atom; D¹ is a carbonyl group or a single bond; B¹ is the divalent azole group selected from thiazolediyl, oxazolediyl, isoxazolediyl or oxadiazolediyl; R¹³ is a lower alkyl group; R¹ and R² are as defined above and the pharmaceutically acceptable acid addition salts.

The compounds of the following formulae are more preferred:



25 wherein X is a hydrogen or halogen atom; B¹, R¹, R², R¹³ are as defined above and the pharmaceutically acceptable acid addition salts.

The compounds of the following formulae are most preferred:



wherein R¹⁴ is hydrogen atom or lower alkyl group; X, B¹, R¹, R² are as defined above and the pharmaceutically acceptable acid addition salts.

The pharmaceutically acceptable acid addition salts of the novel aminoazole derivatives are also embraced by the present invention and are readily prepared by contacting the free base with the appropriate mineral or organic acid in either aqueous solution or in a suitable organic solvent. The solid salt may then be obtained by precipitation or by evaporation of the solvent. The pharmaceutically acceptable acid addition salts of this invention include, but are not limited to, the hydrochloride, hydrobromide, sulfate, phosphate, formate, acetate, fumarate, maleate, malate, tartrate, aspartate, glutamate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, hydroxybenzenesulfonate, dihydroxybenzenesulfonate, and the like.

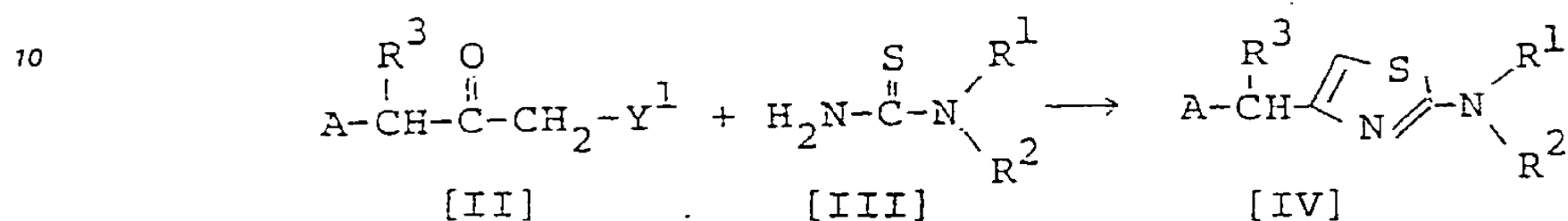
The compounds of this invention include optical isomers, tautomers, all hydrates and crystal forms thereof. The amino azole compounds (I) can be produced by various processes, of which typical examples are set forth below.

Process (A):

The process of the azole (I) comprises cyclization:

The cyclization processes comprise the following five procedures:

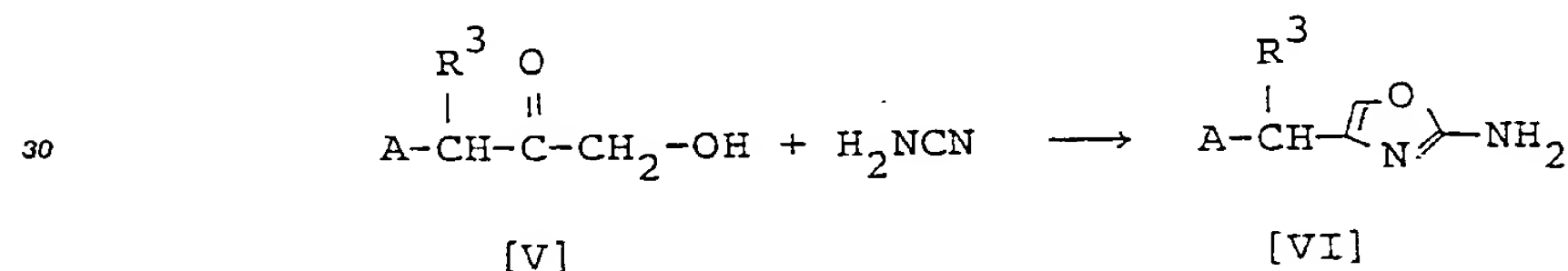
Procedure 1



wherein Y¹ is a leaving group such as halogen (e.g. chlorine, bromine), alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. p-toluenesulfonyloxy), and A, R¹, R² and R³ are as defined above.

The compound (IV) is obtained by reacting the compound (II) with the compound (III) in an inert solvent at room temperature or under heating. As the solvent, there may be used water, alcohols (e.g. methanol, ethanol), ethers (e.g. ethyl ether or tetrahydrofuran), haloalkanes (e.g. dichloromethane, chloroform) or their mixture.

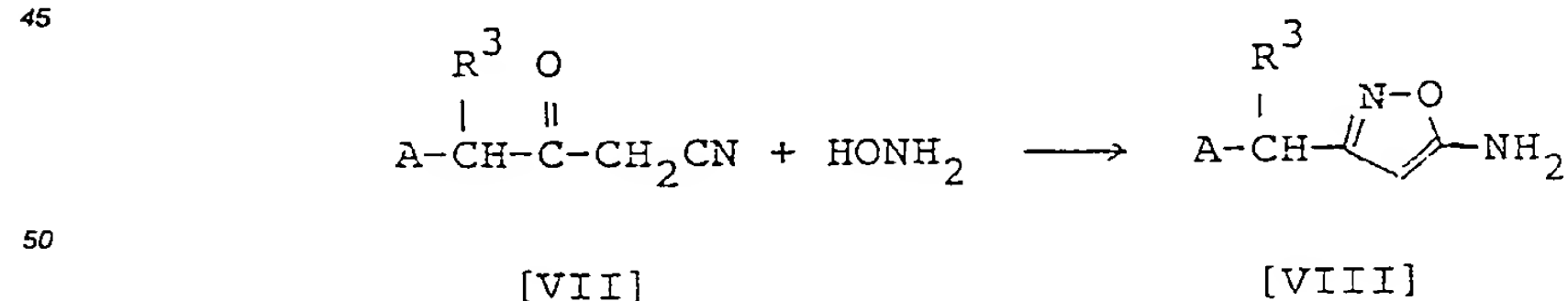
Procedure 2



wherein A and R³ are as defined above.

The compound (VI) is obtained by reacting the compound (V) with cyanamide in an inert solvent at room temperature or under heating in the presence of the base such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate. As the solvent, there may be used alcohols (e.g. methanol, ethanol), ethers (e.g. tetrahydrofuran, 1,4-dioxane), water or their mixture.

Procedure 3



wherein A and R³ are as defined above.

The compound (VIII) is obtained by reacting the compound (VII) with hydroxylamine in an inert solvent at room temperature or under heating. As the solvent, there may be used alcohols (e.g. methanol, ethanol), aromatic hydrocarbons (e.g. benzene, toluene), haloalkanes (e.g. dichloromethane, chloroform), ethers (e.g. tetrahydrofuran, 1,4-dioxane), N,N-dimethylformamide, N,N-dimethylacetamide or pyridine. When using

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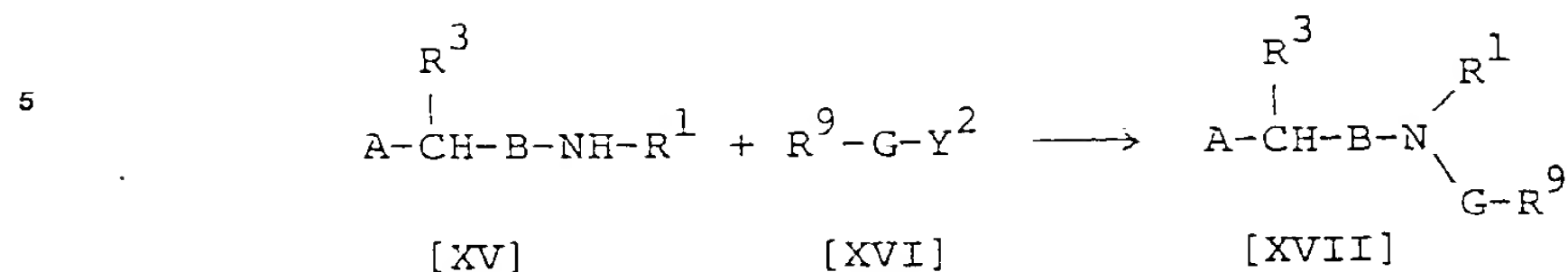
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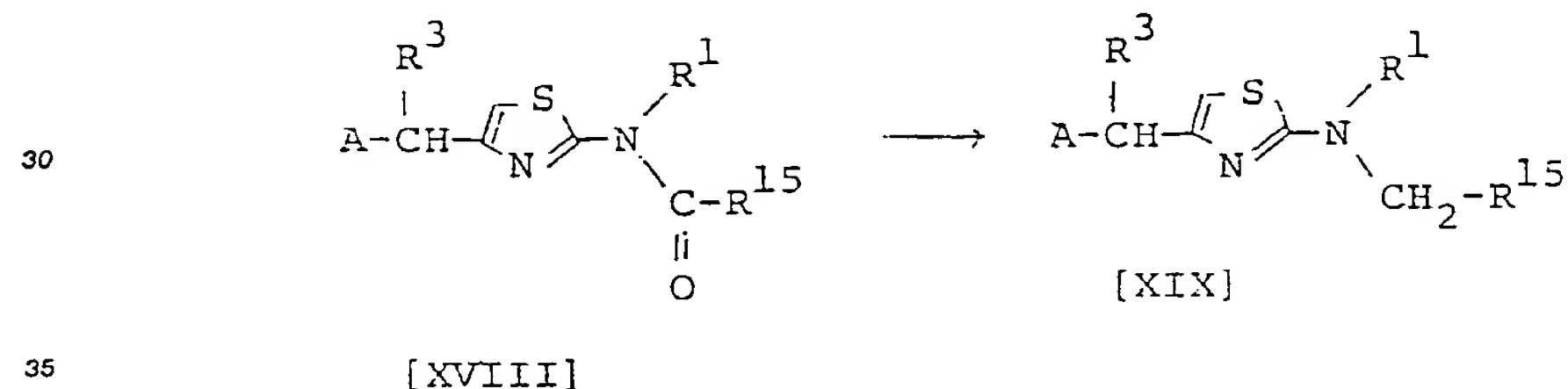
Process (B):



wherein Y² is a leaving group such as halogen (e.g. chlorine, bromine), alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. p-toluenesulfonyloxy), and A, B, G, R¹, R³ and R⁹ are as defined above.

The compound (XVII) is obtained by reacting the compound (XV) with the compound (XVI) in an inert solvent in the presence of an acid-binding agent under conditions ranging from ice-cooling to heating. As the solvent, there may be used aromatic hydrocarbons (e.g. benzene, toluene), haloalkanes (e.g. dichloromethane, chloroform), ethers (e.g. tetrahydrofuran, 1,4-dioxane), N,N-dimethylformamide, N,N-dimethylacetamide or acetone. As the acid-binding agent, there may be used an inorganic base or organic base, examples of which are sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, triethylamine or pyridine. If the reaction is performed under two-phase condition, a phase-transfer catalyst may be effectively used.

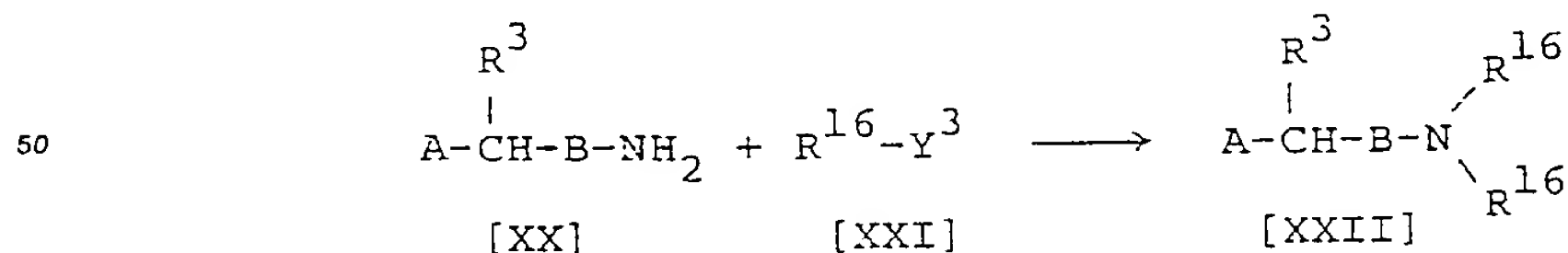
Process (C):



wherein R¹⁵ is lower alkyl, aryl-lower alkyl or aryl and A, R¹ and R³ are as defined above.

The compound (XIX) is obtained by reducing the compound (XVIII) with a metal hydride such as lithium aluminium hydride at a temperature ranging from cooling to heating. As the solvent, there may be used ethyl ethers (e.g. ether tetrahydrofuran).

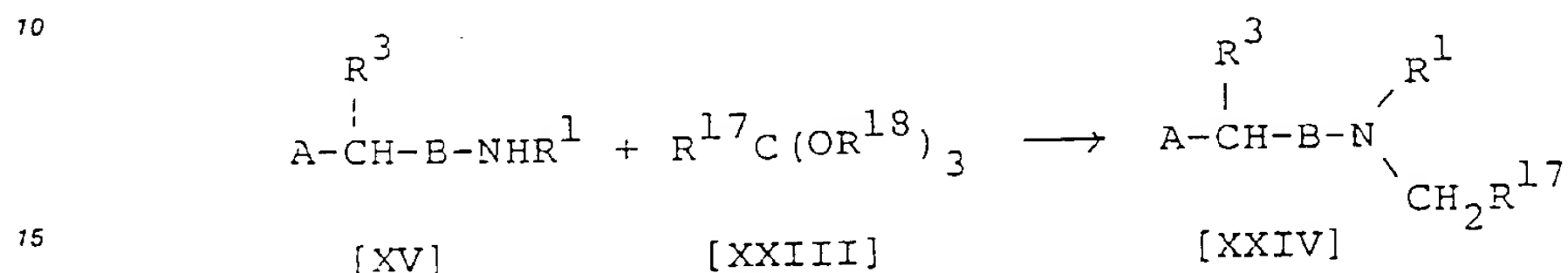
Process (D):



wherein R¹⁶ is lower alkyl or aryl-lower alkyl; Y³ is a leaving group such as halogen (e.g. chlorine, bromine), alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. p-toluenesulfonyloxy) and, A, B and R³ are as defined above.

The compound (XXII) is obtained by reacting the compound (XX) with the compound (XXI) in an inert solvent at a temperature ranging from cooling to heating. As the solvent, there may be preferably used solvent mixtures combining a hydrophobic solvent such as benzene or toluene with an aqueous solution of a strong base. Preferably this reaction is performed at room temperature. As the base, there may be used sodium hydroxide, potassium hydroxide or potassium carbonate.

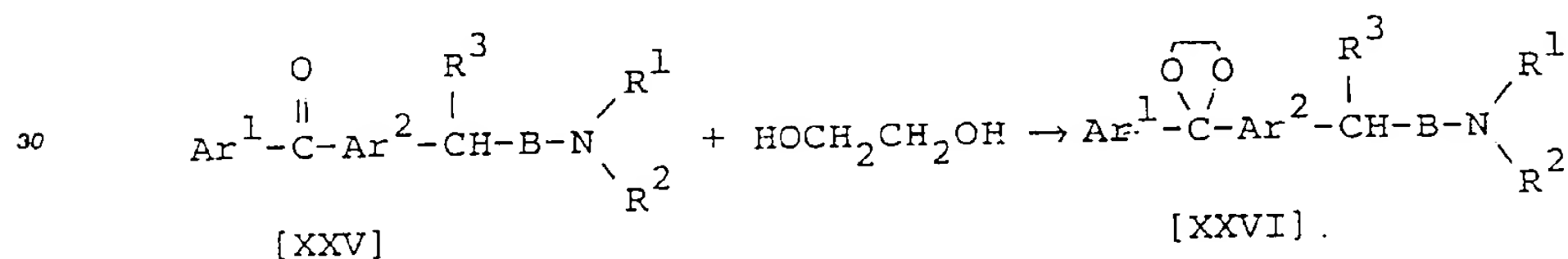
Process (E):



wherein R¹⁷ is hydrogen or lower alkyl, R¹⁸ is a lower alkyl and A, B, R¹ and R³ are as defined above.

The compound (XXIV) is obtained by reacting the compound (XV) with the compound (XXIII) under heating and then reducing it with sodium borohydride in an inert solvent. As the solvent, there may be used alcohols (e.g. ethanol, propanol, isopropanol) or ethers (e.g. ethyl ether, tetrahydrofuran, 1,4-dioxane).

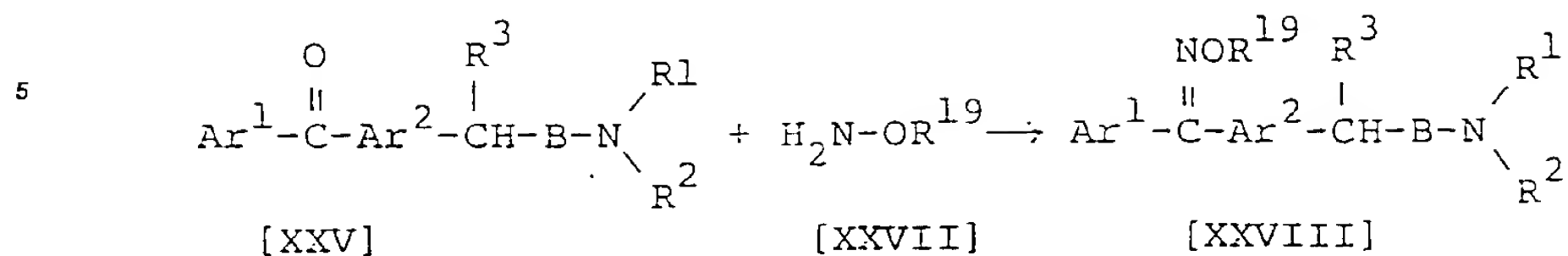
Process (F):



wherein Ar¹, Ar², B, R¹, R² and R³ are as defined above.

The compound (XXVI) is obtained by treating the compound (XXV) with ethyleneglycol in the usual manner (for example "Shin-Jikkenkagaku Kouza" 14, (V), p. 2518, edited by NIHON-KAGAKIKAI). For example, the compound (XXVI) is obtained by heating the compound (XXV) with ethyleneglycol in aromatic hydrocarbons (e.g. benzene, toluene) in the presence of p-toluenesulfonic acid.

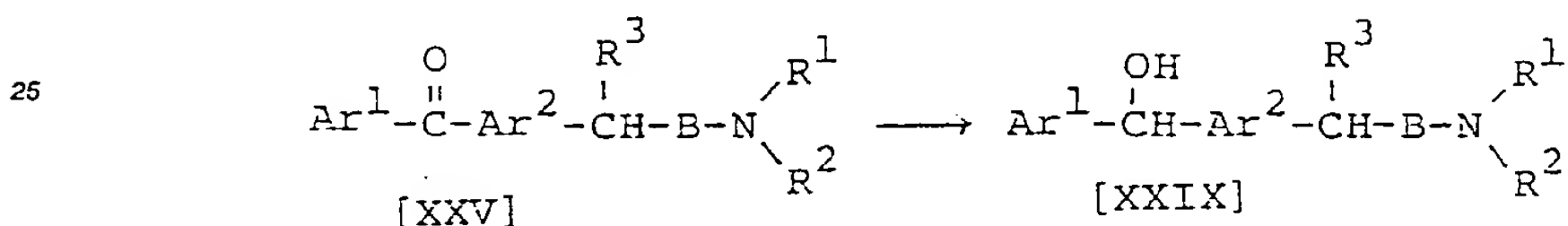
Process (G):



wherein R^{19} is a hydrogen atom or lower alkyl and Ar^1 , Ar^2 , B, R^1 , R^2 and R^3 are as defined above.

The compound (XXVIII) is obtained by reacting the compound (XXV) with the compound (XXVII) in an inert solvent at room temperature or under heating. As the solvent, there may be used alcohols (e.g. methanol, ethanol, propanol, isopropanol), ethers (e.g. tetrahydrofuran, 1,4-dioxane), aromatic hydrocarbons (e.g. benzene, toluene), pyridine or water. This reaction is performed using hydroxylamine-acid salts with an acid-binding agent such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, triethylamine or pyridine.

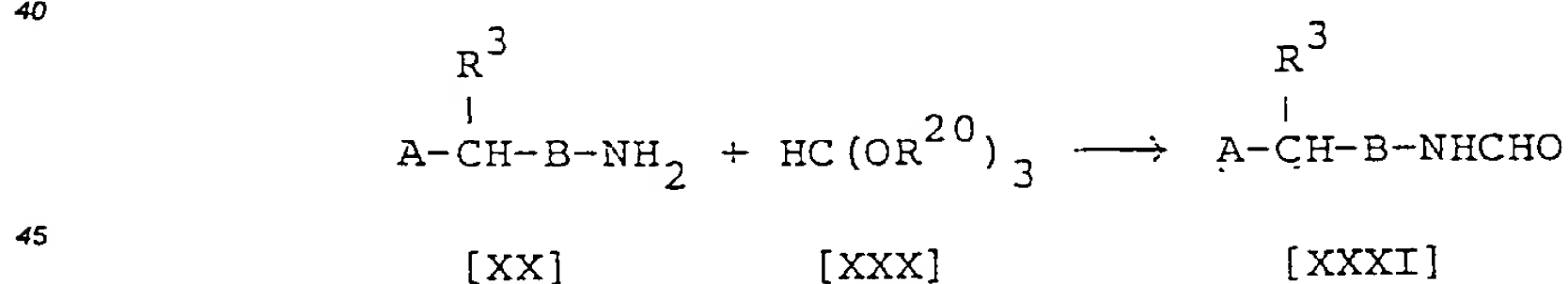
Process (H):



wherein Ar^1 , Ar^2 , B, R^1 , R^2 and R^3 are as defined above.

The compound (XXIX) is obtained by reducing the compound (XXV) with reducing agents such as sodium borohydride in an inert solvent at a temperature from ice-cooling to heating. As the solvent, there may be used alcohols (e.g. ethanol, n-propanol, isopropanol) or ethers (e.g. tetrahydrofuran, ethyl ether, 1,4-dioxane).

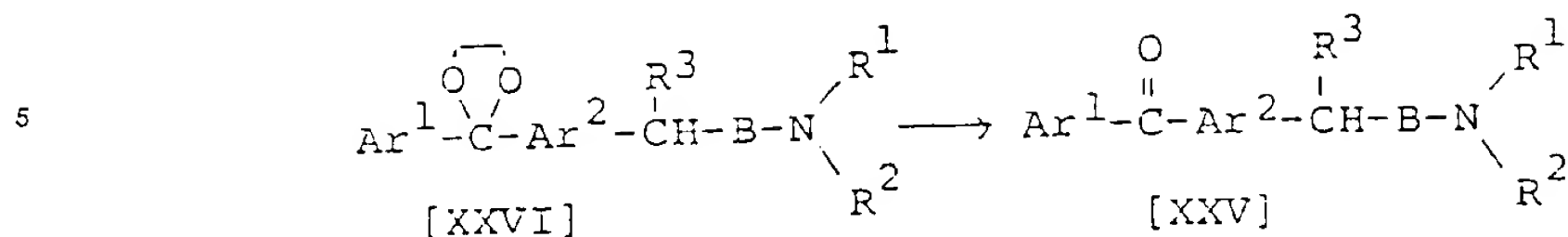
Process (I):



wherein R^{20} is lower alkyl, and A, B and R^3 are as defined above.

The compound (XXXI) is obtained by reacting the compound (XX) with the compound (XXX) under heating, followed by hydrolyzation with an acid catalyst in an inert solvent. As the solvent, there may be used alcohols (e.g. methanol, ethanol, n-propanol, isopropanol), aromatic hydrocarbons (e.g. benzene, toluene), aliphatic hydrocarbons (e.g. hexane, heptane), haloalkanes (e.g. dichloromethane, chloroform), ethyl ether or their mixture. As the acid catalyst, there may be used mineral acid (e.g. hydrochloric acid, sulfuric acid) or silica-gel.

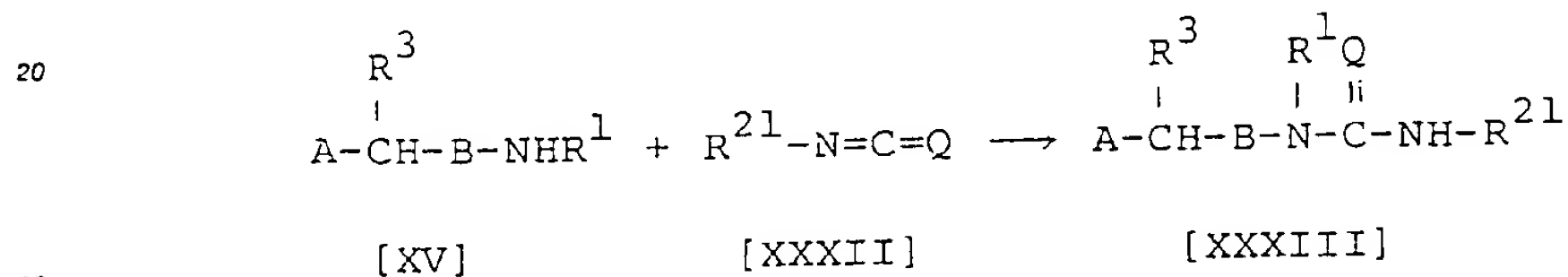
Process (J):



wherein Ar¹, Ar², B, R¹, R² and R³ are as defined above.

The compound (XXV) is obtained by hydrolyzing the compound (XXVI) in the usual manner (for example, Sin-Jikkenkagaku-Kooza 14, (V), p2519, edited by NIHON-KAGAKUKI). For example, the compound (XXV) is obtained by reacting the compound (XXVI) with 80% acetic acid at room temperature.

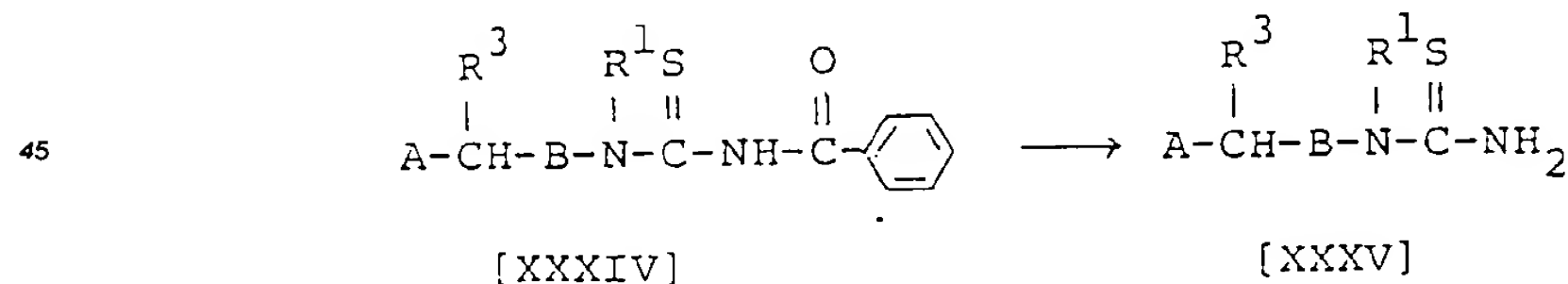
Process (K):



wherein Q is oxygen or sulfur atom, R²¹ is lower alkyl, lower alkenyl, lower cycloalkyl, aryl-lower alkyl, aryl or aroyl group, and A, B, R¹ and R³ are as defined above.

The compound (XXXIII) is obtained by reacting the compound (XV) with the compound (XXXII) in an inert solvent at a temperature ranging from ice-cooling to heating. As the solvent, there may be used alcohols (e.g. methanol, ethanol), aromatic hydrocarbons (e.g. benzene, toluene), ethers (e.g. tetrahydrofuran, 1,4-dioxane), haloalkane (e.g. dichloromethane, chloroform), N,N-dimethylformamide, N,N-dimethylacetamide or acetone. This reaction is preferably performed in the presence of an inorganic base (e.g. sodium carbonate, potassium carbonate, sodium bicarbonate). If necessary, this reaction is performed after the amines (XV) is converted to a metal amide with a metalating agent such as lithium diisopropylamide.

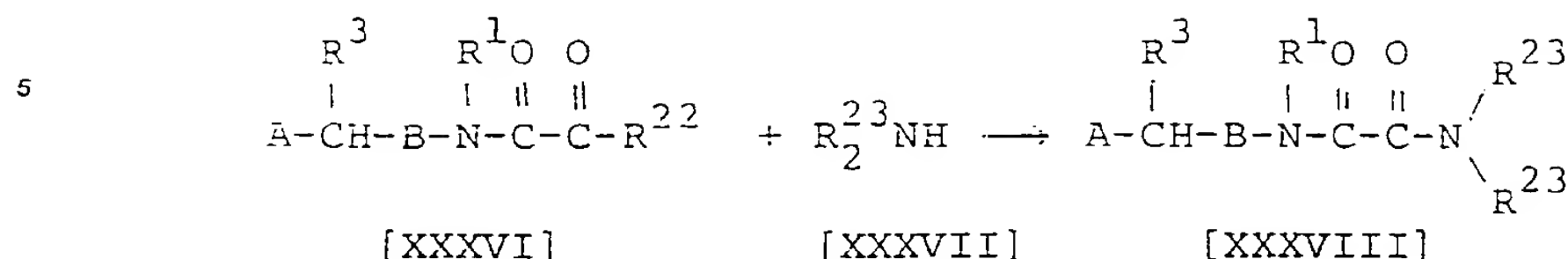
Process (L):



wherein A, B, R¹ and R³ are as defined above.

The compound (XXXV) is obtained by hydrolysis of the compound (XXXIV) in an inert solvent in the presence of a base under heating. As the solvent, there may be used alcohols (e.g. methanol, ethanol), ethers (e.g. tetrahydrofuran, 1,4-dioxane), acetone, water or their mixture. As the base, there may be used sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate.

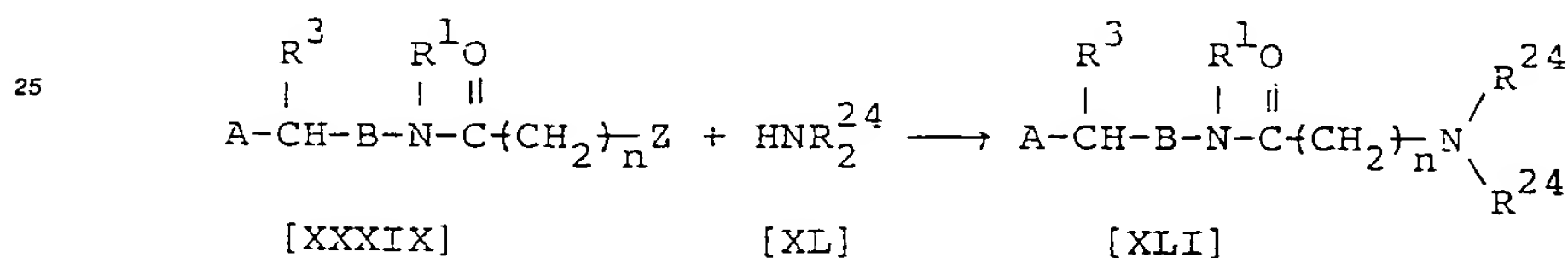
Process (M):



wherein R^{22} is halogen atom (e.g. chlorine, bromine) or lower alkyl group; R^{23} is a hydrogen atom, lower alkyl group or $-\text{NR}_2^{\text{23}}$ is a 5-, 6-, 7-membered saturated heterocyclic ring, and A, B, R^1 and R^3 are as defined above.

The compound (XXXVIII) is obtained by reacting the compound (XXXVI) with the compound (XXXVII) in an inert solvent under heating. As the solvent, there may be used aromatic hydrocarbons (e.g. benzene, toluene), ethers (e.g. tetrahydrofuran, 1,4-dioxane), haloalkanes (e.g. dichloromethane, chloroform) or pyridine.

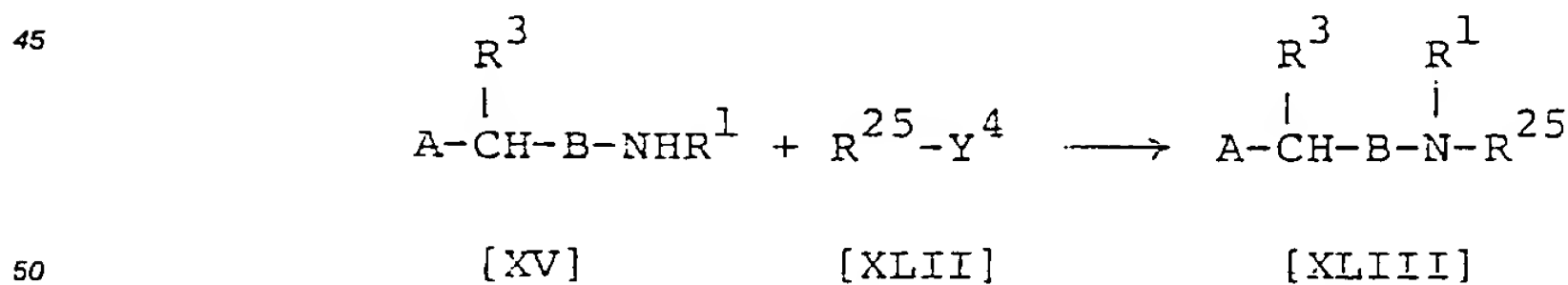
Process (N):



wherein Z is halogen (e.g. chlorine, bromine, iodine), R^{24} is a hydrogen atom and lower alkyl, n is an integer from 1 to 4, and A, B, R^1 and R^3 are as defined above.

The compound (XLI) is obtained by reacting the compound (XXXIX) with the compound (XL) in an inert solvent. As the solvent, there may be used aromatic hydrocarbons (e.g. benzene, toluene), ethers (e.g. tetrahydrofuran, 1,4-dioxane), haloalkanes (e.g. dichloromethane, chloroform), N,N-dimethylformamide, N,N-dimethylacetamide or pyridine. This reaction is effectively performed in the presence of an inorganic or an organic base (e.g. sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, triethylamine or pyridine) at a temperature ranging from ice-cooling to heating.

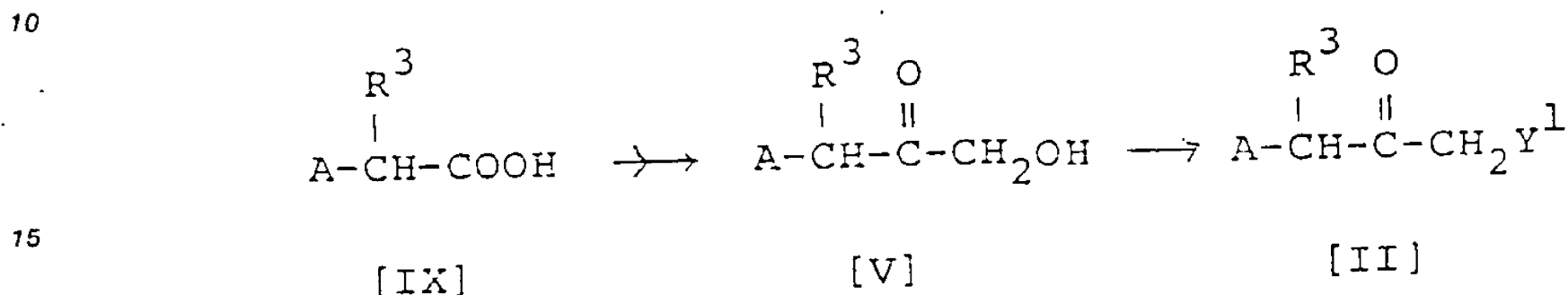
Process (P):



wherein R^{25} is lower alkyl or aryl-lower alkyl; Y^4 is a leaving group such as halogen (e.g. chlorine, bromine), alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. p-toluenesulfonyloxy), and A, B, R^1 and R^3 are as defined above.

The compound (XLIII) is obtained by reacting the compound (XV) with the compound (XLII) in an inert solvent in the presence of a phase-transfer catalyst in addition to a base. As the solvent, there may be used the mixture of hydrophobic solvents (e.g. benzene, toluene) and water. As the base, there may be used sodium hydroxide, potassium hydroxide or potassium carbonate.

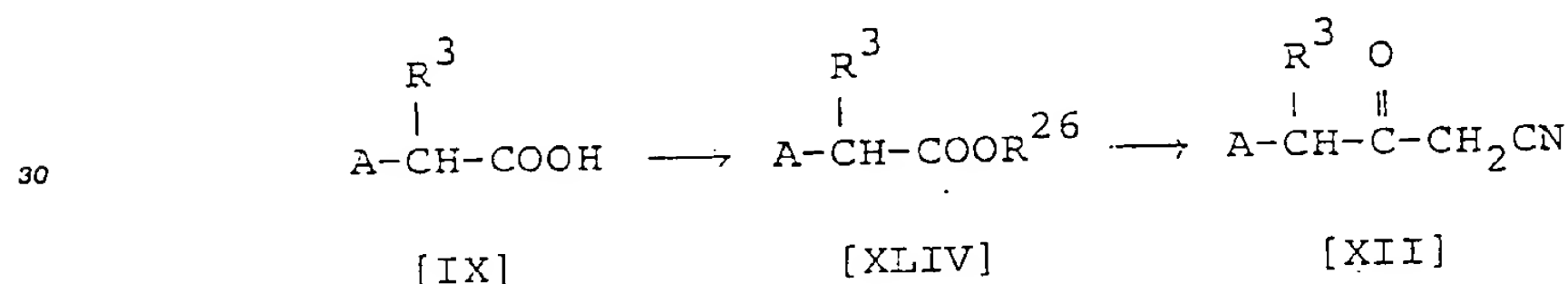
5 The starting compounds (XV), (XVIII), (XX), (XXV), (XXXIV), and (XXXIX) and objective compounds of this invention and obtained by process (A-1), (A-2), (A-3), (A-4), (A-5), (B), (C), (E), (F), (J), (K) and (P). And the compounds (II), (III), (V), (VII), (IX), (X), (XIII), (XVI), (XXI), (XXIII), (XXVII), (XXX), (XXXII), (XXXVII), and (XLI) are known or obtained in a usual manner. For example, the compound (II) and (V) are prepared by the following process.



wherein A, Y¹, and R³ are as defined above.

20 The compound (V) is prepared by reacting the acid chloride of the compound (IX) with tris-(trimethylsilyloxy) ethylene according to the procedure reported in the literature (for example, A. Wissner, J. Org. Chem. 44, (25) 4617 (1979)). The compound (II) is prepared from the compound (V) in the usual manner. For example, the compound (II) (wherein Y¹ is chlorine) is obtained by substitution of the hydroxy group by a chlorine atom using the triphenylphosphinecarbon tetrachloride system.

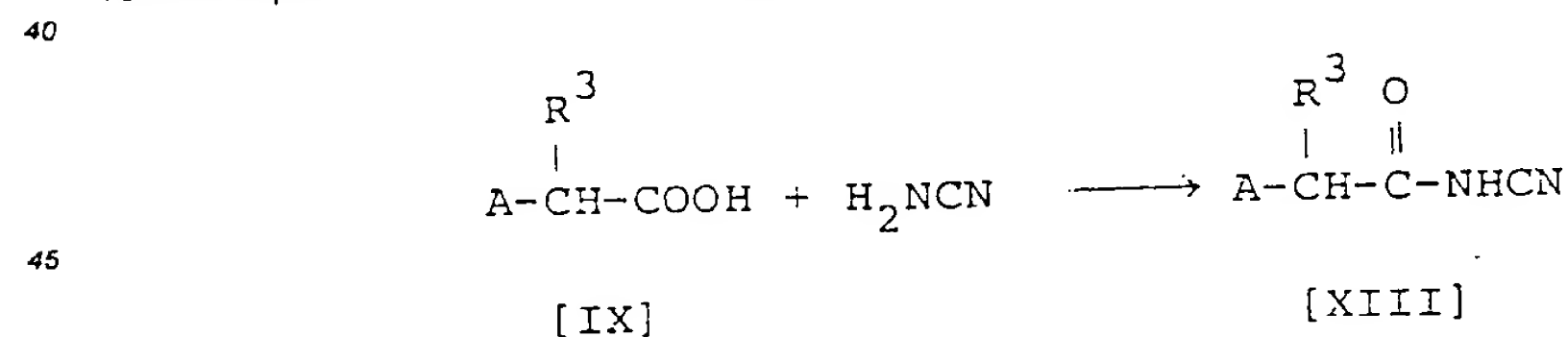
25 The compound (XII) is prepared by the following procedure.



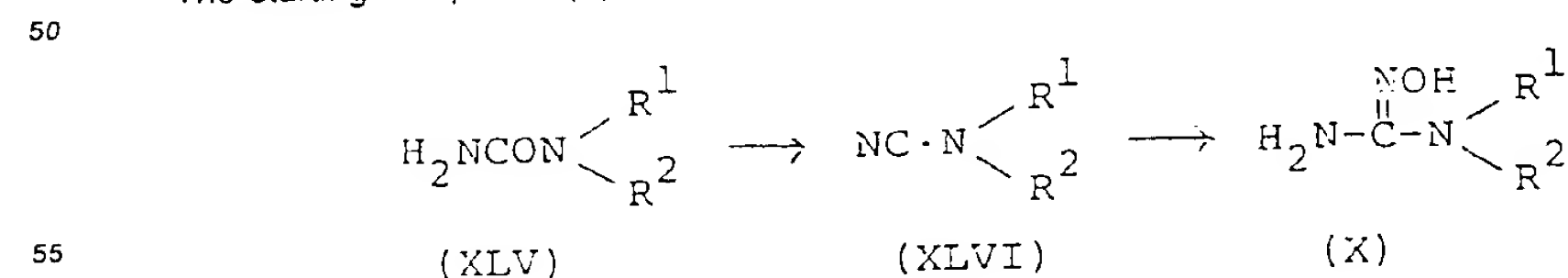
35 wherein R²⁶ is lower alkyl and A and R³ are as defined above.

The compound (XLIV) is obtained by esterification of the compound (IX) in the usual manner and the compound (VII) is obtained by base-catalytic condensation of the compound (XLIV) with acetonitrile.

The compound (XIII) is prepared by reacting the compound (IX) with cyanamide in an inert solvent at room temperature or under heating according to the procedure reported in D.E. Pat. No. 2,843,887.



50 The starting compound (X) is known or obtained by the following process:

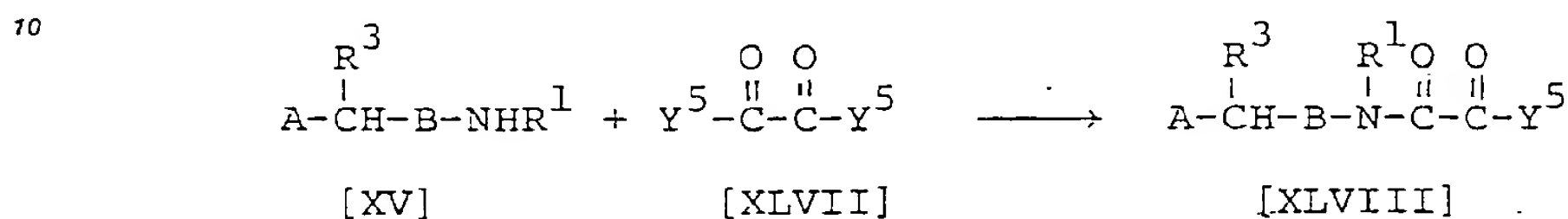


wherein R¹ and R² are as defined above.

The compound (XLVI) is obtained by dehydrating the compound (XLV) according to procedure reported in the literature (for example, W. Schroth et al, Journal f. prakt. chemie, Band 325, Heft5, 1983, s 787-802).

The compound (X) is obtained by reacting the compound (XLVI) with hydroxylamine according to the procedure reported in the literature (BETZECKI et al, Bull. Acad. Pol. Sci. Ser Sci. Chem., vol 18, No 8, 431 (1970)).

The compound (XXXVI) is obtained by the following process; when R²² is a halogen atom, the compound (XLVII) is prepared by reacting the compound (XV) with the compound (XLVII) in inert solvent at room temperature or under heating.



wherein Y⁵ is a halogen atom (e.g. chlorine, bromine), and A, B, R¹ and R³ are as defined above. When R²² is a lower alkoxy group, the compound (XXXVI) is obtained by process (B).

As stated above, the aminoazoles (I) of this invention are pharmaceutically effective especially in the case of autoimmune diseases. The facts are well evidenced by the pharmacological test data as set forth below.

Test method:

[Rat-Adjuvant Arthritis Test]

Rat adjuvant arthritis test is one of a few and most useful pharmacological model for the investigation of human chronic inflammations. It is known that the effective compounds in this model system are useful for the treatment of rheumatoid arthritis, such as steroids or non-steroidal anti-inflammatory drugs (Oyo Yakuri, 5, 169 (1971)).

According to the method of Winter et al., Arth. Rheum., 9, 394 (1966), male Sprague-Dawley rats, 6 weeks of age, were given subplantar injection of the adjuvant consisting of 1 mg of killed *Mycobacterium butyricum* (Difco) and 0.2 ml of liquid paraffin. After fourteen days the rats with established arthritis were treated with the drug as follows: the test compound was suspended in 5% gum arabic solution and orally given once a day for 5 days, day 15 to day 19. Control rats were given gum arabic in the same way. On day 19, the volume of the right foot was determined with a plethysometer. The lowest dose producing a significant reduction (p < 0.001) of the foot volume compared to that of the control group was regarded as minimum effective dose (MED).

[Mice-Arthus Test]

It is thought that rheumatoid arthritis is a disease with immunity disorders and one origin of this disease is the Arthus reaction induced by immune complex (Ivan M. Roitt, 1980, "Essential Immunology"). The effect on rheumatoid arthritis may be estimated by the effect of the Arthus reaction.

According to the method of Abe et al., Enshou, 1, 739 (1981), male BABL/c mice, 6 weeks of age, were sensitized by injection of 8 x 10⁷ sheep red blood cells (SRBC) (Nihon Bio-Sap. Center) in 0.2 ml of phosphate buffered saline (PBS) into the tail vein. Two weeks later, the mice were boosted by the i.v. injection of 8 x 10⁷ SRBC and 5 day later the animals were challenged by the subcutaneous injection of 1 x 10⁸ SRBC in 25 μl of PBS into the right hind footpad. The swelling following the SRBC-injection into the right hind paw and contralateral left hind paw were measured with micrometer 3hr after the challenge. The difference between these two measurements is regarded as the oedema due to the Arthus reaction. The percentage inhibition of the reaction was determined by comparison with the positive control group. The test compounds were administered orally 24hr and 1hr before the challenge. The results of two tests with the compounds of examples, 2, 7, 9, 11, 21, 22, 48, 67, 74 are shown in Table 1.

Table 1 - Results of Rat-Adjuvant Arthritis Test and

Mice-Arthus Test

Example No.	Structure	Minimum Effective Dose (mg/kg)	
		Adjuvant Arthritis	Arthus
2		25	10
7		10	10
9		10	50
11		2.5	10
21		2.5	10
22		2.5	50
48		10	50
67		10	50
74		2.5	50

- Cont'd -

Table 1 (Cont'd)

5	levamisole	non-effective at 50 mg/kg	50
	D-Penicillamine	non-effective at 200 mg/kg	non-effective at 50 mg/kg

10

The compounds of this invention are effective in both the rat adjuvant arthritis test and mice Arthus reaction test, on the other hand, levamisole is ineffective against rat adjuvant arthritis and D-penicillamine is ineffective against both rat adjuvant arthritis and mice Arthus reaction. Therefore, the compounds of this invention are useful therapeutic agents for treating rheumatoid arthritis. That is to say, the compounds of this invention are effective in the treatment of not only rheumatoid arthritis but also immunity disorders.

15

In addition, the compounds of this invention also improve several immunological factors of spontaneous autoimmune diseases in animals (MRL/1 mice). The results obtained suggest a potential role for the compounds of this invention in the treatment of autoimmune disease in human, e.g. rheumatoid arthritis.

20

Additionally, the compounds of this invention are effective as 5-lipoxygenase inhibitor as set forth below.

Test method:

25

[5-Lipoxygenase Inhibitory Test]

30

According to the method of Harvey et al., J. Pharmacol. Meth., 9, 147-155 (1983), polymorphonuclear leukocytes (PMNs) from Hartley guinea pigs weighting 280 to 350 g were elicited by intraperitoneal injection of 2% casein suspension (10ml/100g guinea pig weight), and collected 16-18 hrs later. The cells were washed with saline and finally suspended at 2.39×10^7 cells/ml in Krebs Ringer Bicarbonate buffer (KBR) pH 7.4.

35

935 μ l of PMNs were aliquoted into 15 ml glass tubes and prewarmed to 37°C in a shaking water bath. Drugs (10 μ l of dimethylsulfoxide (DMSO)) were added 10 minutes prior to the addition of 1- 14 C-arachidonic acid (New England Nuclear Co.; 50 μ l of 2 μ Ci/ml KBR) and calciumionophor, A23187 (Calbiochem Boehringer Co.; 5 μ l of 1 mg/ml DMSO). The reaction was terminated after a further 10 min by the addition of 0.2 M citric acid (100 μ l). Unstimulated controls were also included to determine the increased metabolism of arachidonic acid due to A23187. Samples were diluted with water (4 ml) and extracted twice with ethyl acetate (5 ml). The ethyl acetate was concentrated under a stream of nitrogen and two-thirds of the residue was applied to TLC plates. The plates were developed in toluene : dioxane : acetic acid = 65 : 34 : 1.5 at 10°C.

40

Radiochromatographic analysis of the labelled metabolites of [14 C] arachidonic acid was performed with a Berthold LB283 TLC Linear Analyzer. In samples and controls, the ratio of radioactivity of 5-HETE in metabolites to all of metabolites of [14 C] arachidonic acid was calculated, and the results were determined as percent inhibition calculated from these ratios

45

50

55

$$\text{Inhibition (\%)} = \frac{\text{Ratio of radioactivity of control} - \text{Ratio of radioactivity of sample}}{\text{Ratio of radioactivity of control}} \times 100$$

Inhibition (%)	<20%	-
	20-40%	+
	40-70%	++
	70% <	+++

Results of 5-lipoxygenase inhibition for compounds of example 21, 22, 65 and 67 are shown in Table 2.

Table 2 Results of 5-Lipoxygenase Inhibitory Test

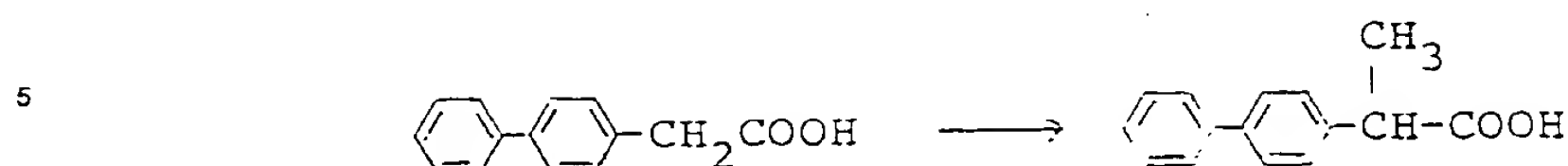
<u>Example No.</u>	<u>Activity of Inhibition</u>
21	++
22	+++
65	+++
67	+++

The above results show that the compounds of this invention possess 5-lipoxygenase inhibitory activity and, therefore, they may be useful for treating allergies and inflammations, e.g. allergic asthma and allergic rhinitis.

The compounds (I) of present invention may be used in the form of pharmaceutical compositions adapted to enteral or parenteral administration. Accordingly, for oral administration the compounds may be combined in a conventional manner with a suitable solid or liquid carrier or diluent to form tablets, capsules, powders, syrups, solutions, suspensions and the like. For parenteral administration the compounds may be combined with sterile aqueous or organic media to form injectable solutions or suspensions. The compounds may be administered to the rectum as suppositories.

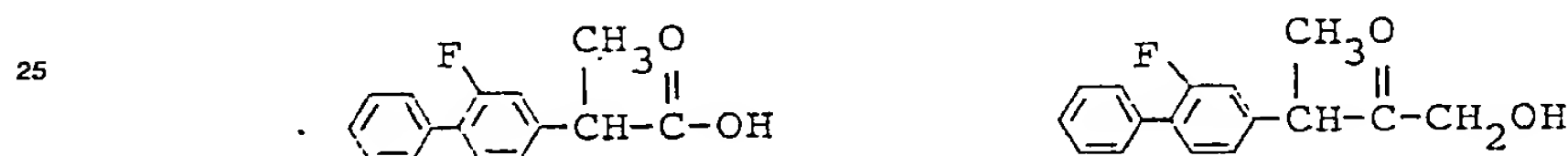
In man, the compounds of this invention may generally be administered in an amount of from about 5 mg/day to 2000 mg/day, preferably about 25 mg/day to 1000 mg/day, depending upon the symptom, the route of administration, and the particular compound of the invention. The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

Reference Example 1



10 In usual manner, lithium diisopropylamide in tetrahydrofuran was prepared with diisopropylamine (3.2 ml, 22.6 mmol) and 1.6 M n-butyllithium in hexane (14.2 ml, 22.6 mmol). ("Reagents for Organic Synthesis", 2, p. 249) To this lithium diisopropylamide in tetrahydrofuran was added dropwise 4-biphenylacetic acid (2.40 g, 11.3 mmol) in tetrahydrofuran at from -50°C to -30°C. After the mixture was reacted at from -40°C to -10°C for 2 h, to the mixture was added dropwise methyl iodide (1.77 g, 12.4 mmol) in tetrahydrofuran, then the temperature was raised at from -30°C to room temperature in nature. After the mixture was stirred for 4 h, was added water and was adjusted at pH 2 with 3 N sulfonic acid, then extracted with ether. After the ether extract was dried over, then the extract was evaporated under reduced pressure to a residue, which was chromatographed to afford 2-(4-biphenyl)propionic acid (2.38 g, 93% yield) as white crystalline material: mp 144-145°C.

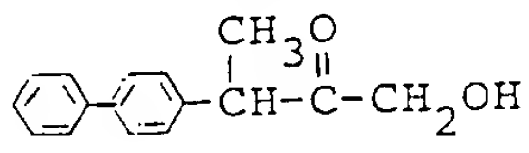
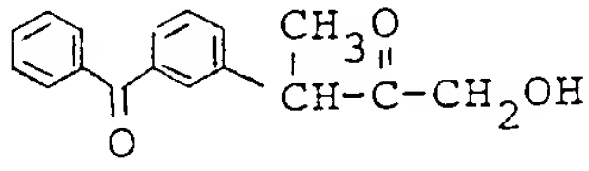
Reference Example 2



30 To thionyl chloride (40 ml) was added 2-(2-fluoro-4-biphenyl) propionic acid (10.0 g, 40.9 mmol) by portions with stirring at room temperature. After the addition, the mixture was stirred over night at room temperature, and the solution was evaporated under reduced pressure to afford the acid chloride. After tris-(trimethylsilyloxy)ethylene (35.9 g, 123 mmol) was added to the acid chloride at room temperature, the mixture was stirred at 95°C for 4 h, then cooled to room temperature. After the addition of dioxane (53.5 ml) and then 0.6 N hydrochloric acid (21.5 ml) dropwise to the mixture, the solution was stirred at 85°C for 30 min, then cooled to room temperature, saturated with sodium chloride, and extracted with ether. The ether extracts were washed with water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to a residue, which was chromatographed to afford 3-(2-fluoro-4-biphenyl)-2-oxo-1-butanol (10.0 g, 95% yield) as crystalline material: mp 63-64.5°C, NMR(CDCl₃) δ 1.48(d, 3H), 2.97(t, 1H), 3.80(q, 1H), 4.25-4.0 (d, 2H), 6.93-7.62(m, 8H) ppm; IR(neat) 3450, 1725, 1610, 1480, 1420, 1270 cm⁻¹.

40 According to substantially the same procedure as that of Reference Example 2, the following compounds were made.

Table 3

Ref. Ex. No.	Structure	Physical Data
3		mp. 87.5~89.0°C
4		NMR(CDCl ₃) δ 1.49 (d, 3H), 2.97 (t, 1H), 3.85 (q, 1H), 4.20 (d, 2H), 7.22-7.82 (m, 9H) ppm; IR(neat) 3480, 1720, 1660, 1600, 1320, 1280 cm ⁻¹

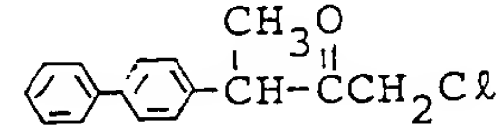
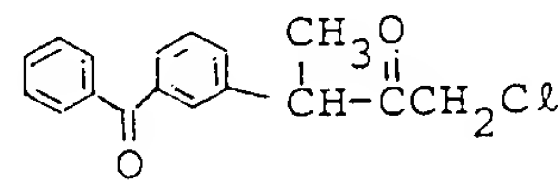
Reference Example 5



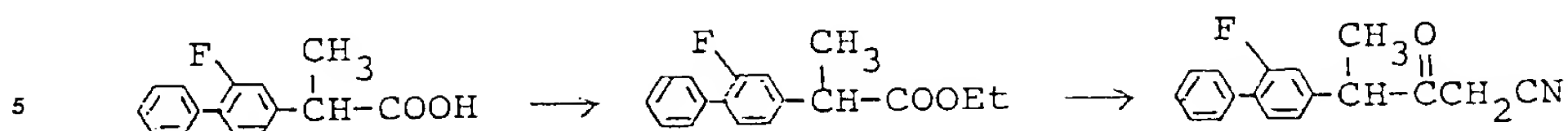
To 3-(2-fluoro-4-biphenyl)-2-oxo-1-butanol (2.00 g, 7.74 mmol) in carbon tetrachloride (5 ml) was added triphenylphosphine (2.15 g, 8.20 mmol) at room temperature. After the addition, the mixture was stirred over night at room temperature, then concentrated to give triphenylphosphine oxide as precipitates. After filtration of the precipitates, the filtrates were evaporated under reduced pressure to a residue, which was chromatographed to afford 1-chloro-3-(2-fluoro-4-biphenyl)-2-butanone (1.01 g, 47% yield) as crystalline materials: mp 57-59°C; NMR(CDCl₃) δ 1.48(d, 3H), 4.07(m, 3H), 6.93-7.63(m, 8H); IR(neat) 1740, 1620, 1480, 1420, 1270 cm⁻¹.

According to substantially the same procedure as that of Reference Example 5, the following compounds were made.

Table 4

Ref. Ex. No.	Structure	Physical Data
6		mp. 101.0~102.5°C
7		NMR(CDCl ₃) δ 1.54 (d, 3H), 4.06 (s, 2H), 4.13 (q, 1H), 7.30~7.90 (m, 9H) ppm; IR(neat) 1735, 1660, 1600, 1320, 1280 cm ⁻¹

Reference Example 8



10 To 2-(2-fluoro-4-biphenyl)-propionic acid (30.0 g, 0.123 mol) in ethanol (300 ml) was added conc. sulfonic acid (3.0 g). After the addition, the mixture was stirring at 50°C for 5 h, then concentrated and extracted with benzene. The benzene extracts were washed with aqueous sodium hydrogen carbonate solution then with water, and dried over. The extracts were evaporated under reduced pressure to afford ethyl-2-(2-fluoro-4-biphenyl)propionate (33.6 g, 0.123 mol) as oily residue.

15 After 60% sodium hydride (6.5 g, 0.163 mmol) was suspended in tetrahydrofuran under nitrogen atmosphere, the mixture was refluxed for 0.5 h, then added dropwise acetonitrile (7.6 g, 0.185 mol) and ethyl-2-(2-fluorop-4-biphenyl)-propionate described above in tetrahydrofuran (100 ml). After refluxed for 2 h, the mixture was cooled at room temperature and added isopropylalcohol. After stirring for a while, the mixture was evaporated under reduced pressure to a residue, which was made acid with 2N hydrochloric acid and extracted with chloroform. The extracts were washed with water, dried over, and evaporated under reduced pressure to a residue, which was chromatographed and recrystallized with ethanol to afford 4-(2-fluoro-4-biphenyl)-3-oxo-pentanenitril (18.0 g, 55% yield) as pale yellow crystalline material: mp 84-85°C.

20 According to substantially the same procedure as that of Reference Example 8, the following compound was made.

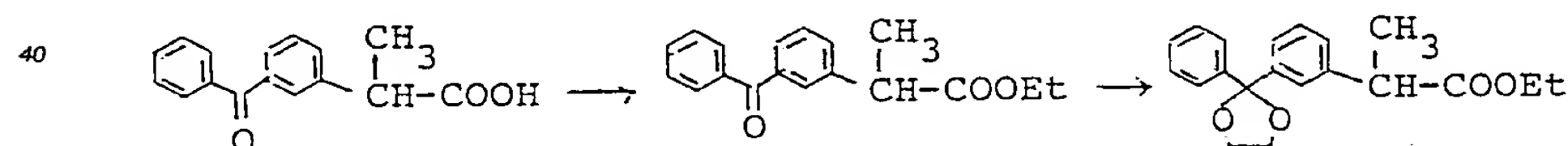
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Table 5

Ref. Ex. No.	Structure	Physical Data
30 9		NMR(CDCl ₃) δ 3.16(s, 2H), 3.91(s, 2H), 7.25~7.66(m, 9H) ppm; IR(neat) 2260, 1730, 1380, 1350, 1120 cm ⁻¹

35

Reference Example 10



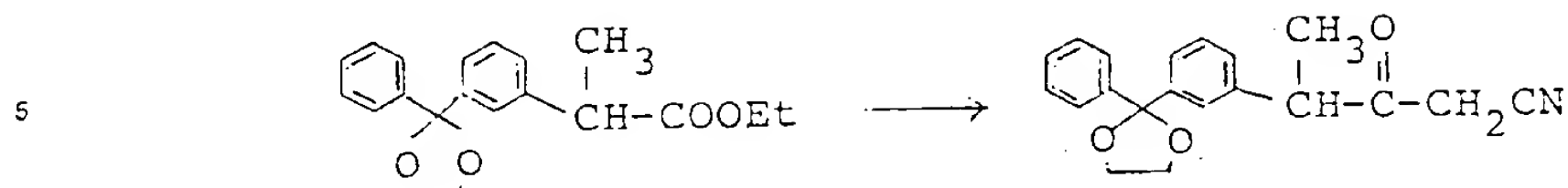
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According to substantially the same procedure as that of Reference Example 8, ethyl 2-(3-benzoylphenyl) propionate (quantitative yield) was obtained from 2-(3-benzoylphenyl) propionic acid (30 g, 0.118 mol).

50 To ethyl 2-(3-benzoylphenyl) propionate in toluene (200 ml), was added ethylene glycol (20.0 g) and p-toluenesulfonic acid monoh-drate (1.0 g). After refluxed for 13 h, the mixture was cooled at room temperature and extracted with benzene. The extracts were washed with aqueous sodium hydrogen carbonate solution and then with water, and evaporated under reduced pressure to a residue, which was chromatographed to afford ethyl 2-(3-(2-phenyl-1,3-dioxolan-2-yl)phenyl) propionate (29.0 g, 75% yield) as oily residue: NMR(CDCl₃) δ 1.15 (t, 3H), 1.47(d, 3H), 3.68(q, 2H), 4.02(s, 4H), 4.07(q, 1H), 7.16-7.85(m, 9H) ppm; IR(neat) 3050, 1740, 1605, 1180, 1080 cm⁻¹.

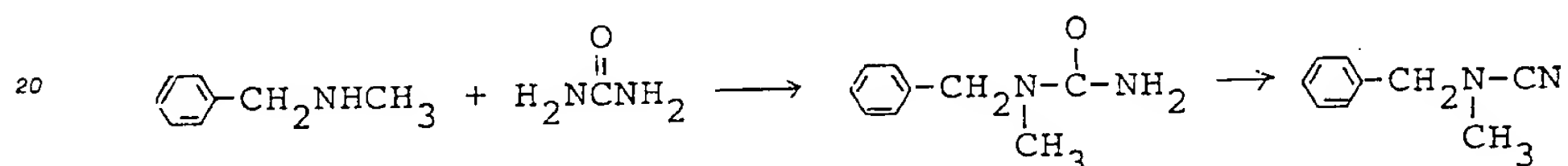
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Reference Example 11



10 According to substantially the same procedure as that of Reference Example 8, with ethyl 2-(3-(2-phenyl-1,3-dioxolan-2-yl)phenyl)propionate (38.5 g, 118 mmol) was obtained 4-(3-(2-phenyl-1,3-dioxolan-2-yl)-phenyl)-3-oxo-pentanenitrile (12.1 g, 32% yield) as pale yellow oily substance: NMR(CDCl₃) δ 1.41(d, 3H), 3.28(s, 2H), 3.85(q, 1H), 4.03(s, 4H), 7.00-7.60(m, 9H) ppm; IR(neat) 2900, 2250, 1730, 1600, 1170, 1080 cm⁻¹.

Reference Example 12



25 To N-methylbenzylamine (12.1 g, 0.1 mol) was added urea (6.0 g, 0.1 mol). After stirred at 118°C for 4 h, the mixture was cooled to room temperature. The solidified mixture was ground to a powder, washed with n-hexane and recrystallized with ethyl acetate to afford N-methyl-N-benzylurea (12.3 g, 75% yield): mp 125-129°C.

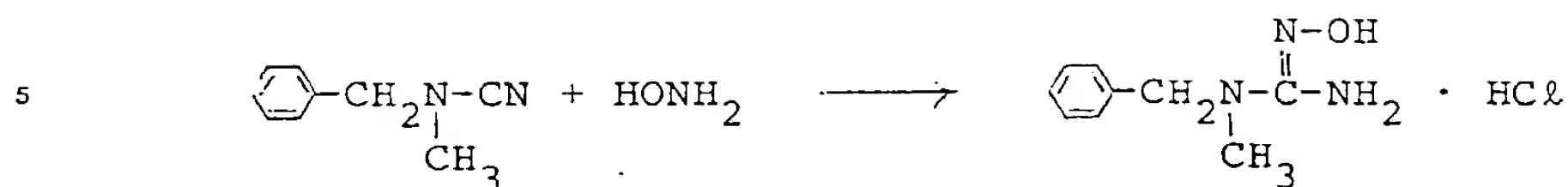
30 To N-methyl-N-benzylurea (1.64 g, 0.01 mol) in chloroform (24ml) and 50% aqueous sodium hydroxide solution (5.4 ml) was added triethylamine (0.1 g, 0.001 mol) and the mixture was vigorously stirred at room temperature for 3.5 h. After addition of water and chloroform, the mixture was stirred, then extracted with chloroform. The extracts were washed with water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to a residue, which was chromatographed to afford N-methyl-N-benzylcyanamide (1.2 g, 82% yield) as oily substance: NMR(CDCl₃) δ 2.77(s, 3H), 4.14(s, 2H), 7.25-7.50(m, 5H); IR(neat) 2220, 1495, 1455, 1365, 730 cm⁻¹.

35 According to substantially the same procedure as that of Reference Example 12, the following compound was made.

Table 6

Ref. Ex. No.	Structure	Physical Data
13		b.p. 80~84°C/10mmHg; NMR(CDCl ₃) δ 1.91(t, 4H), 3.39(t, 4H) ppm; IR(neat) 2200, 1455, 1350 cm ⁻¹

Reference Example 14



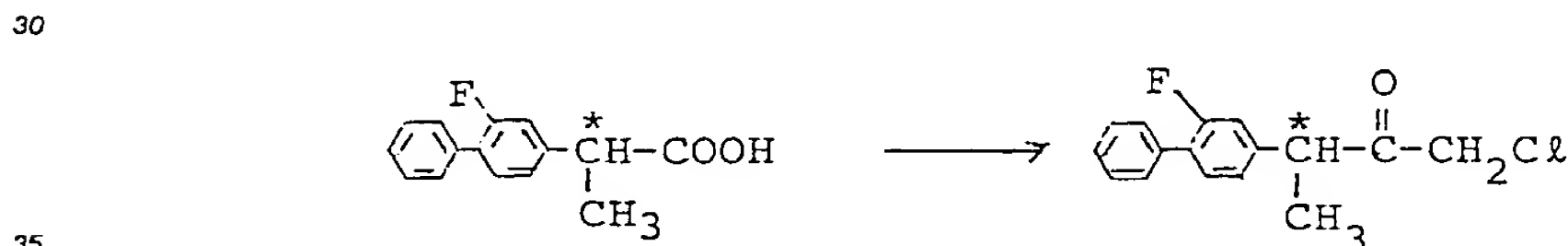
10 To N-methyl-N-benzylcyanamide (10.6 g, 7.3 mmol) in ethanol (10 ml) was added hydroxylamine (0.528 g, 7.3 mmol). After reflux with stirring for 8 h, the mixture was evaporated under reduced pressure to a residue, which was recrystallized with mixture solution of isopropylalcohol and isopropylether to afford 1-methyl-1-benzyl-2-hydroxyguanidine hydrochloride (1.02 g, 65% yield) as crystalline material: mp 111-114°C.

15 According to substantially the same procedure as that of Reference Example 14, the following compound was made.

Table 7

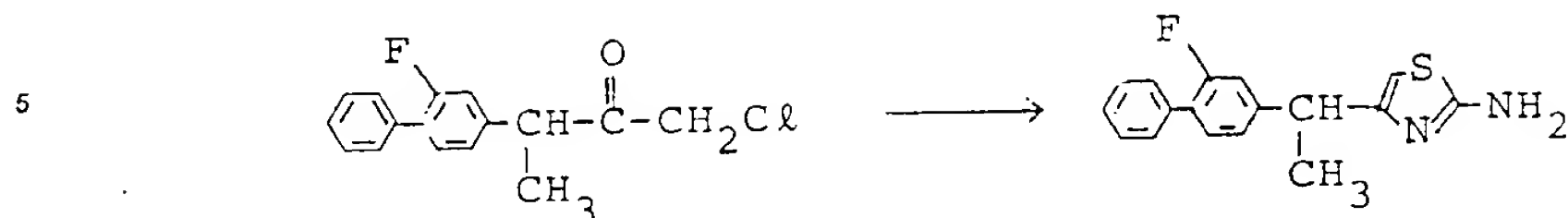
20 Ref. Ex. No.	Structure	Physical Data
15	$ \begin{array}{c} \text{N-OH} \\ \parallel \\ (\text{CH}_3)_2\text{N}-\text{C}-\text{NH}_2 \cdot \text{HCl} \end{array} $	mp. 220°C (decomposition)

Reference Example 16



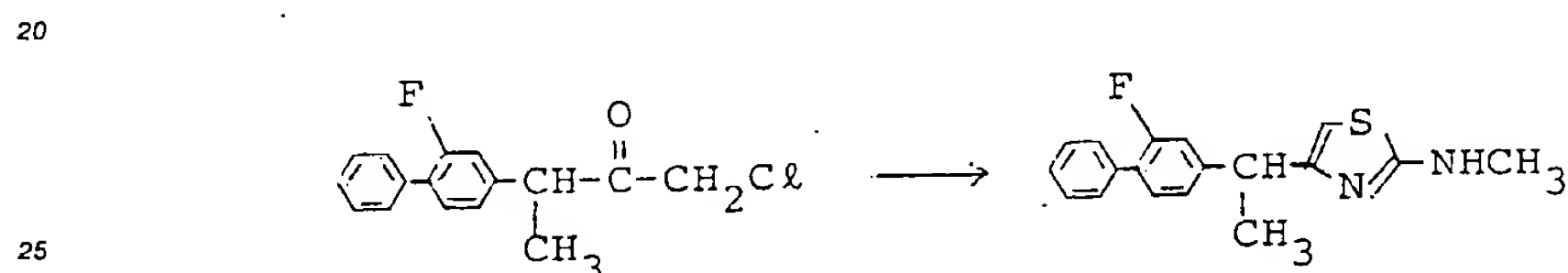
35 (+)-2-(2-Fluoro-4-biphenyl)propionic acid (94.9% ee) was obtained by method of patent (Japan Kokai 53-112841). A solution of diazoketone in ether which was obtained by reaction of (+)-2-(2-fluoro-4-biphenyl)propionic acid (200 mg, 0.82 mmol) obtained above with diazomethane by usual manner [W.E. Bachmann, W.S.Struve, Org. React., 1, 38 (1942)] was bubbled hydrogen chloride gas for 5 minute. The reaction mixture was washed with NaHCO₃ aq. and dried with magnesium sulfate. After evaporation, the residue was chromatographed to afford (+)-1-chloro-3-(2-fluoro-4-biphenyl)-2-butanone (71.5 mg, 75% yield): (α)_D^{25°C} + 180° (c=0.744, CHCl₃)

Example 1



10 To thiourea (1.77 g, 23.3 mmol) in water (50 ml) was added 1-chloro-3-(2-fluoro-4-biphenyl)-2-butanone (5.25 g, 19.0 mmol). After addition, the mixture was heated for 3 hr, and the solution was cooled to room temperature, then added 1N sodium hydroxide to pH 8. The mixture was extracted with chloroform and the chloroform extracts were washed with water, dried over, and evaporated under reduced pressure to a residue, which was chromatographed to afford 2-amino-4-[1-(2-fluoro-4-biphenyl)ethyl] thiazole (4.12 g, 73% yield) as crystalline material: mp 167-168°C.

Example 2



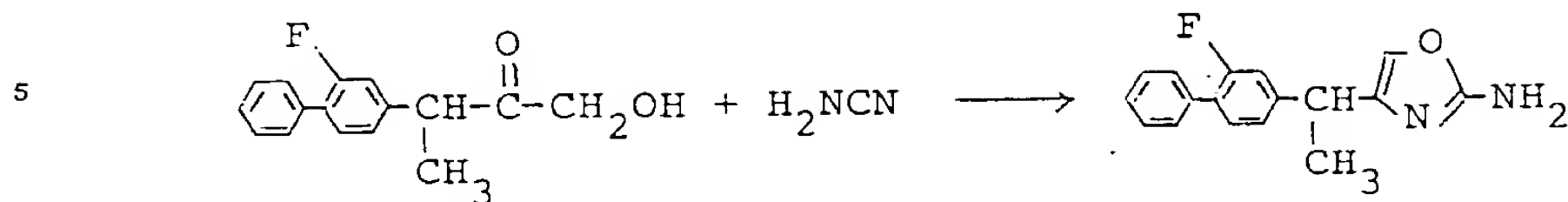
30 To N-methylthiourea (5.55 g, 61.6 mmol) in water was heated with 1-chloro-3-(2-fluoro-4-biphenyl)-2-butanone (16.50 g, 59.6 mmol) at 90°C for 3 hr. Treatment in same manner of Example 1 to give 4-[1-(2-fluoro-4-biphenyl)ethyl]-2-methylaminothiazole (13.15 g, 71% yield): mp 129-129.5°C.

According to substantially the same procedure as that of Example 1, there were obtained the thiazole derivatives of the formula (IV) as listed in Table 8.

Table 8

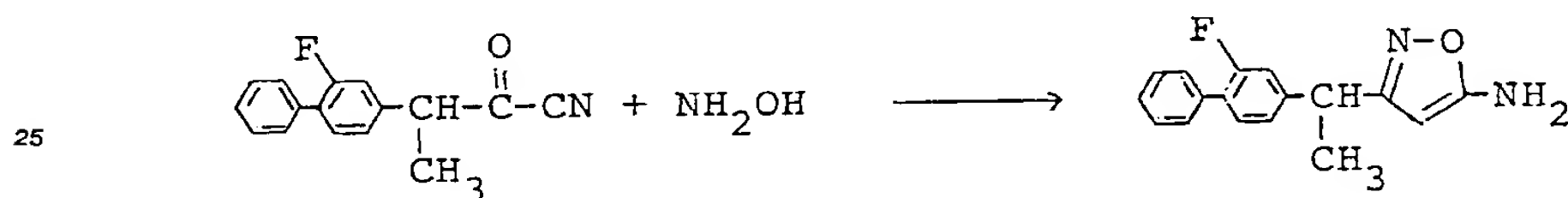
Example	Structure	Physical Data
3		123.0-124.5°C
4		136-137°C
5		121-122°C
6		163.0°C

Example 7



10 To 3-(2-Fluoro-4-biphenyl)-2-oxo-1-butanol (3.57 g, 13.8 mmol) in tetrahydrofuran (35 ml) was added cyanamide (3.65 g, 77.6 mmol) in water and 2N-sodium hydroxide to pH 10. After the addition, the mixture was stirred overnight, then cyanamide (3.65 g, 77.6 mmol) was added to the reaction mixture to pH 10, the mixture was stirred overnight. The reaction mixture was extracted with ether and the extracts were washed with water, dried over and evaporated under reduced pressure to a residue, which was chromatographed to afford 2-Amino-4-(1-(2-fluoro-4-biphenyl)ethyl)oxazole as crystalline material (1.05 g, 27% yield): mp 150.5-151.5°C.

20 Example 8



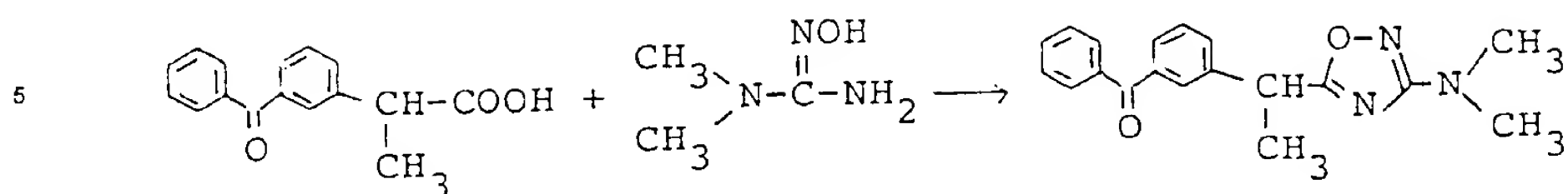
30 To 4-(2-Fluoro-4-biphenyl)-3-oxo-pentanenitrile (2.75 g, 10.3 mmol) in ethanol (70 ml) was added hydroxylamine hydrochloride (1.1 g, 15.8 mmol) in pyridine (10 ml). After addition, the mixture was stirred at room temperature overnight, then evaporated under reduced pressure to a residue, which was chromatographed and then recrystallized to afford 5-amino-3-(1-(2-fluoro-4-biphenyl)ethyl)isoxazole (2.20 g, 76% yield) as crystalline material: mp 122-123°C.

35 According to substantially the same procedure as that of Example 8, there were obtained the isoxazole derivatives of the formula (VIII) as listed in Table 9.

Table 9

Example	Structure	Physical Data
9		138.5-139.0°C
10		145.5-146.0°C

Example 11



10 To the mixture of 2-(3-benzoylphenyl) propionic acid (3.00 g, 11.8 mmol), 1,1-dimethylamino-2-hydroxyguanidine hydrochloride (1.98 g, 14.2 mmol), N-hydroxybenztriazole (1.91 g, 14.2 mmol) and dicyclohexylcarbodiimide (2.92 g, 14.2 mmol) in N,N-dimethylformamide (100 ml) were added triethylamine (1.43 g, 14.2 mmol). After the addition, the mixture was stirred at room temperature for 12 hr, then filtered.

15 The filterates were evaporated under reduced pressure to a residue, which was chromatographed to afford 3-(3-benzoylphenyl)-5-(1,1-dimethylamino)-1,2,4-oxadiazole (2.00 g, 53% yield); NMR (CDCl₃) δ 1.27(d, 3H), 3.00(s, 6H), 4.32(q, 1H), 7.30-7.99(m, 9H) ppm; IR(neat) 1660, 1595, 1400, 1280 cm⁻¹.

According to substantially the same procedure as that of Example 10, there were obtained the oxadiazole derivatives of the formula (XI) as listed in Table 10.

Table 10

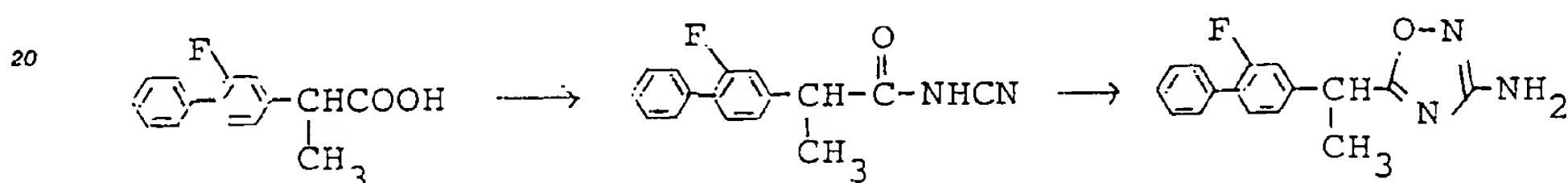
Example	Structure	Physical Data
12		NMR(CDCl ₃) δ 3.00 (s, 6H), 4.13 (s, 2H), 7.33-7.93 (m, 9H) ppm; IR(neat) 1660, 1600, 1400, 1280 cm ⁻¹
13		mp 65-67°C
14		mp 60-61°C
15		mp 109.5-110.5°C
16		mp 128.0-128.5°C
17		mp 114.0-114.5°C
18		mp 116.5-117.0°C
19		NMR(CDCl ₃) δ 1.72 (d, 3H), 1.94 (m, 4H), 3.41 (m, 4H), 4.34 (q, 1H), 7.30-8.11 (m, 9H) ppm; IR(neat) 1660, 1595, 1410, 1285 cm ⁻¹

- Cont'd -

Table 10 (Cont'd)

5	20		NMR (CDCl ₃) δ 1.71 (d, 3H), 2.93 (s, 3H), 4.26 (q, 1H), 4.57 (s, 2H), 7.05-7.60 (m, 13H) ppm; IR (neat) 1595, 1485, 1455, 1410, 1265 cm ⁻¹
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Example 21



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A mixture of 2-(2-fluoro-4-biphenyl)propionic acid (5.00 g, 20.5 mmol) and thionyl chloride (10 ml) in benzene (50 ml) was stirred under reflux for 4 hr and the solution was evaporated under reduced pressure to afford the acid chloride. After the acid chloride was dissolved in acetone (15 ml), the solution was added to cyanamide (1.44 g, 30.8 mmol) in 2N-NaOH (16 ml) by portions at 0-5°C. The mixture was controlled above pH 10 by 2N-NaOH during addition. After the addition, the mixture was stirred at room temperature for 15 hr, then diluted with water, acidified with 1N-HCl to pH 6 and extracted with ether. The water phase was acidified with 1N-HCl to pH 3 and then extracted with chloroform. The chloroform extracts were washed with saturated NaCl aq., dried with magnesium sulfate, then evaporated under reduced pressure to a residue, which was chromatographed to afford N-(2-(2-fluoro-4-biphenyl)propionyl)cyanamide. To hydroxylamine hydrochloride (2.20 g, 30.4 mmol) in pyridine (5 ml) was added N-(2-(2-fluoro-4-biphenyl)propionyl)cyanamide in ethanol (15 ml) by portion under cooling for 15 minute and the mixture was stirred at room temperature for 1 hr, then stood at room temperature overnight. To the reaction mixture was added 2N-NaOH (40 ml) to afford the precipitates. The precipitates were collected, washed with water, dried and recrystallized with ethyl acetate to afford 3-amino-5-(1-(2-fluoro-4-biphenyl)ethyl)-1,2,4-oxadiazole (3.00 g, 52% yield): mp 174.5-175.0°C.

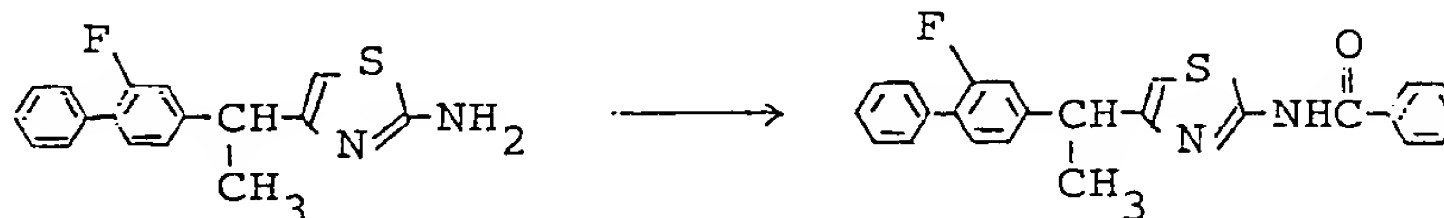
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According to substantially the same procedure as that of Example 21, there were obtained the oxadiazole derivatives of the formula (XIV) as listed in Table II.

Table 11

Example	Structure	Physical Data
22		mp 122.0-123.0°C
23		mp 173.0-174.0°C

Example 24



To 2-amino-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (300 mg, 1.01 mmol) in tetrahydrofuran (15 ml) was added benzoyl chloride (145 mg, 1.03 mmol) and triethylamine (101 mg, 1.00 mmol) and the mixture was stirred at room temperature overnight. After reaction, the reaction mixture was filtered and evaporated under reduced pressure to a residue, which was chromatographed to afford 2-benzamido-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (279 mg, 69% yield): mp 147-147.5°C.

According to substantially the same procedure as that of Example 24, there were obtained the azole derivatives of the formula (XVII) as listed in Table 12.

Table 12

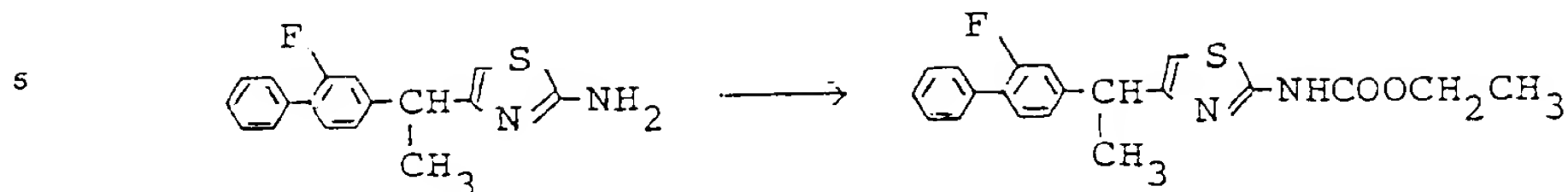
Example	Structure	Physical Data
25		mp 126.5-128.0°C
26		mp 159.0-160.0°C
27		mp 143.0-143.5°C
28		mp 162.5-163.5°C

- Cont'd -

Table 12 (Cont'd)

29		NMR (CDCl ₃) δ 1.67 (d, 3H), 3.09 (t, 2H), 3.77 (s, 3H), 3.89 (t, 2H), 4.21 (q, 1H), 6.65 (s, 1H), 7.05-7.56 (m, 8H) ppm; IR (neat) 1660, 1485, 1430, 1285, 1115, 755, 695 cm ⁻¹
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Example 30



To 2-amino-4-(1-(2-fluoro-4-biphenyl)ethyl)-thiazole (5.00 g, 1.68 mmol) in tetrahydrofuran (150 ml) was added ethyl chloroformate (1.82 g, 16.8 mmol) and triethylamine (1.70 g, 16.8 mmol) and the mixture was stirred under reflux for 2 hr. After cooling, the reaction mixture was diluted with water, then extracted with ethyl acetate. The extracts were washed with 1N-HCl and water, dried, then evaporated under reduced pressure to a residue, which was chromatographed to afford 2-ethoxycarbonylamino-4-(1-(2-fluoro-4-biphenyl)ethyl) thiazole (3.954 g, 64% yield): NMR(CDCl₃) δ 1.31(t, 3H), 1.60(t, 3H), 4.25(m, 3H), 6.58(s, 1H), 6.95-7.58(m, 8H) ppm; IR(nujol) 3280, 1720, 1290, 1230, 1080 cm⁻¹.

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According to substantially the same procedure as that of Example 30, there were obtained the azole derivatives of the formula (XVII) as listed in Table 13.

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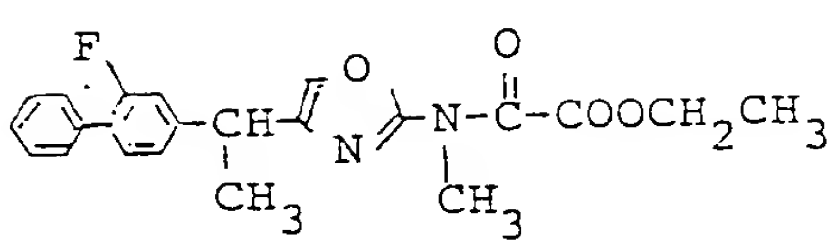
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Table 13

Example	Structure	Physical Data
31		NMR(CDCl ₃) δ1.62 (d, 3H), 4.20 (q, 1H), 4.85 (s, 2H), 6.60 (s, 1H), 6.90-7.58 (m, 8H), 9.12 (m, 1H) ppm IR(nujol) 1750, 1560, 1380, 1280 cm ⁻¹
32		mp. 104.0-105.0°C
33		mp 93.5-94.5°C
34		NMR(CDCl ₃) δ1.25 (t, 3H), 1.71 (d, 3H), 4.26 (q, 3H), 5.98 (s, 1H), 6.94-7.58 (m, 8H) ppm; IR(neat) 1810, 1775, 1620, 1240, 1100 cm ⁻¹
35		mp 136.0-136.5°C
36		NMR(CDCl ₃) δ1.41 (t, 3H), 1.68 (d, 3H), 3.68 (s, 3H), 4.24 (q, 1H), 4.43 (q, 2H), 6.73 (s, 1H), 7.07-7.55 (m, 8H) ppm; IR(neat) 1745, 1670, 1520, 1490, 1440, 1420, 1285, 1240, 1100, 1070, 760 cm ⁻¹
37		mp 123.5-125.0°C

- Cont'd -

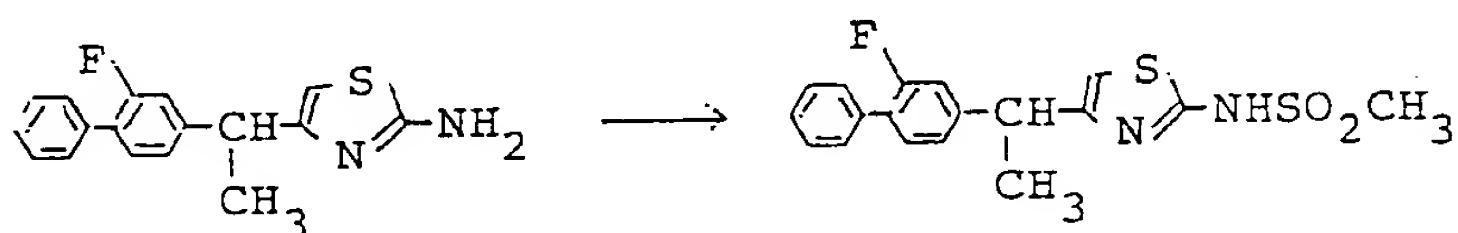
Table 13 (Cont'd)

5	38		NMR (CDCl ₃) δ 1.22 (t, 3H), 1.58 (d, 3H), 3.40 (s, 3H), 4.15 (q, 2H), 4.98 (q, 1H), 7.02-7.55 (m, 9H) ppm; IR (neat) 1750, 1700, 1600, 1420, 1220, 1140 cm ⁻¹
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Example 39

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To a mixture of 2-amino-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (500 mg, 1.68 mmol) and triethylamine (340 mg, 3.36 mmol) in tetrahydrofuran was added methanesulfonyl chloride (385 mg, 3.36 mmol) by portion and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with water, extracted with ethyl acetate and evaporated under reduced pressure to a residue, which was chromatographed and then recrystallized to afford 2-methanesulfonylamino-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (447 mg, 71% yield): mp 127.5-129.0°C.

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According to substantially the same procedure as that of Example 39, there were obtained theazole derivatives of the formula (XVII) as listed in Table 14.

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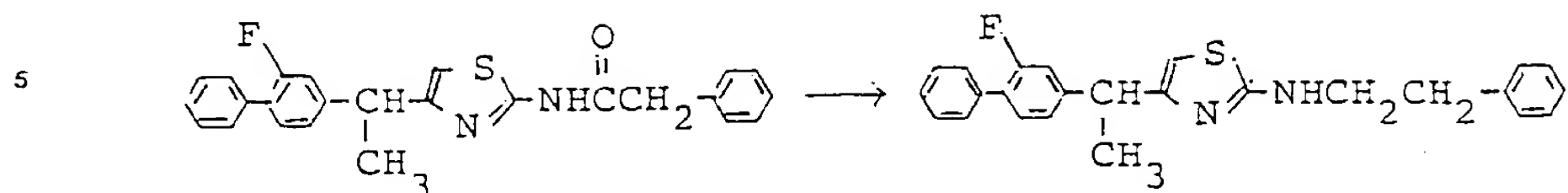
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Table 14

Example	Structure	Physical Data
40		mp 111.0-114.0°C
41		mp 163.0-164.0°C
42		mp 170.5-172.0°C
43		NMR (CDCl ₃) δ 1.65 (d, 3H), 4.12 (q, 1H), 4.32 (s, 2H), 5.45 (s, 1H), 7.06-7.56 (m, 8H) ppm; IR (neat) 1600, 1560, 1410, 1350 cm ⁻¹
44		NMR (CDCl ₃) δ 1.67 (d, 3H), 3.32 (s, 3H), 4.18 (q, 1H), 5.99 (s, 1H), 6.99-7.74 (m, 8H) ppm; IR (neat) 1590, 1480, 1420, 1365, 1175, 1070, 985, 835, 750, 725 cm ⁻¹
45		NMR (CDCl ₃) δ 1.59 (d, 3H), 3.27 (s, 3H), 3.41 (s, 3H), 4.01 (q, 1H), 7.05-7.55 (m, 9H) ppm; IR (neat) 1590, 1360, 1160, 980, 880, 850 cm ⁻¹
46		NMR (CDCl ₃) δ 1.64 (d, 3H), 2.97 (s, 3H), 4.06 (q, 1H), 4.73 (q, 2H), 7.09-7.56 (m, 14H) ppm; IR (neat) 1590, 1360, 1170, 970, 850 cm ⁻¹

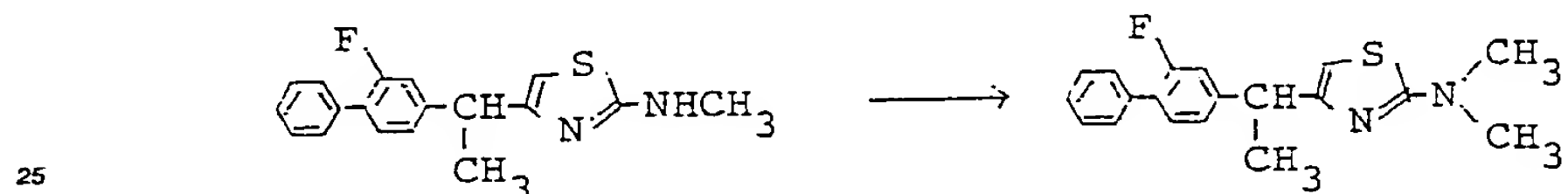
Example 47



10 To 2-phenylacetamido-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (1.00 g, 2.51 mmol) in tetrahydrofuran (20 ml) was added lithium aluminum hydride (150 mg) by portion, then the mixture was refluxed for 2 hr. After cooling, the reaction mixture was filtered and evaporated under reduced pressure to a residue. The residue was extracted with chloroform and the extracts were washed with water, dried, then evaporated
15 under reduced pressure to a residue, which chromatographed and recrystallized to afford 4-(1-(2-fluoro-4-biphenyl)ethyl)-2-phenethylaminothiazole (504 mg, 50% yield): mp 74.5-75.5°C

Example 48

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30 To 4-(1-(2-fluoro-4-biphenyl)ethyl)-2-methylaminothiazole (415 mg, 1.33 mmol) in benzene (6 ml) was added methyl iodide (370 mg, 2.61 mmol), tetra-n-butyl ammonium hydrogen sulfate (435 mg, 1.33 mmol) and 50% NaOH aq. (3 ml), then the mixture was stirred at room temperature overnight. The reaction mixture was diluted with water, then acidified with 2N-HCl to pH 6 and the aqueous solution was extracted with benzene. The extracts were washed with water, dried and then evaporated under reduced pressure to a residue, which chromatographed to afford 4-(1-(2-fluoro-4-biphenyl)ethyl)-2-dimethylaminothiazole (369
35 mg, 85% yield): NMR(CDCl₃) δ 1.62(d, 3H), 3.06(s, 6H), 4.09(q, 1H), 6.06(s, 1H), 7.02-7.63(m, 8H) ppm; IR-(neat) 2950, 1620, 1550, 1420, 1340 cm⁻¹.

According to substantially the same procedure as that of Example 48, there were obtained theazole derivatives of the formula (XLV) as listed in Table 15.

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Table 15

Example	Structure	Physical Data
49		mp 87.0-88.0°C
50		NMR (CDCl ₃) δ 0.97 (t, 3H), 1.60 (d, 3H), 1.60-1.69 (m, 2H), 3.10-3.18 (m, 2H), 4.06 (q, 1H), 5.12-5.30 (m, 1H), 6.15 (s, 1H), 7.02-7.54 (m, 8H) ppm; IR (neat) 3200, 1620, 1340, 1260 cm ⁻¹
51		NMR (CDCl ₃) δ 1.26 (d, 6H), 1.60 (d, 3H), 3.45-3.62 (m, 1H), 4.05 (q, 1H), 5.50-5.80 (m, 1H), 6.12 (s, 1H), 7.03-7.54 (m, 8H) ppm; IR (nujol) 3300, 1630, 1380, 1270 cm ⁻¹

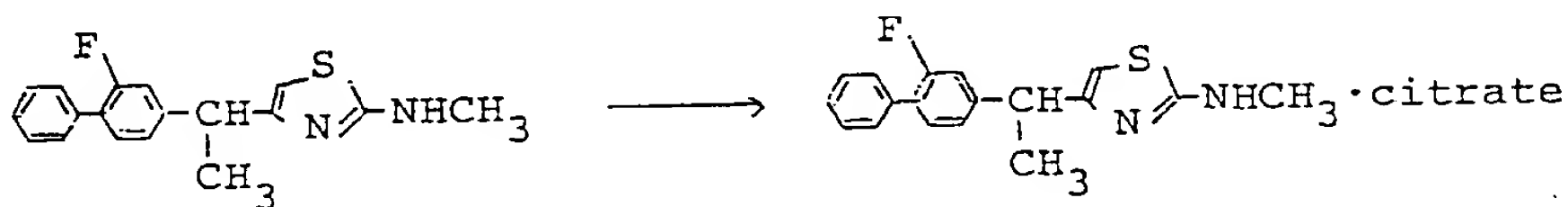
- Cont'd -

Table 15 (Cont'd)

5	52		NMR (CDCl ₃) δ 0.94 (t, 3H), 1.33-1.47 (m, 2H), 1.61 (d, 3H), 1.56-1.66 (m, 2H), 3.16-3.21 (m, 2H), 4.06 (q, 1H), 5.30-5.52 (m, 1H), 6.15 (s, 1H), 7.03-7.54 (m, 8H) ppm; IR (nujol) 3400, 1600, 1380, 1340, 1270 cm ⁻¹
15	53		mp 102.5-103.5°C
20	54		NMR (CDCl ₃) δ 1.56 (d, 3H), 3.77 (s, 6H), 4.02 (s, 4H), 4.03 (q, 1H), 4.52 (s, 1H), 7.15-7.60 (m, 9H) ppm; IR (neat) 2970, 1610, 1430, 1210 cm ⁻¹
25	55		mp 89.0-90.0°C
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35			

Example 56

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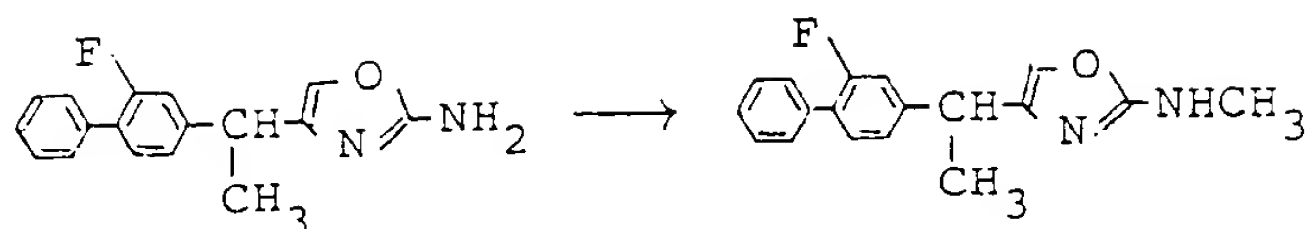


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To 4-(1-(2-fluoro-4-biphenyl)ethyl)-2-methylaminothiazole (200 mg, 0.64 mmol) in methanol was added citric acid (60 mg, 0.64 mmol) in methanol and the mixture was stirred at room temperature, then evaporated under reduced pressure to a residue, which was recrystallized to afford 4-(1-(2-fluoro-4-biphenyl)ethyl)-2-methylamino-thiazole citrate: mp 150-151°C.

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Example 57



A mixture of 2-amino-4-(1-(2-fluoro-4-biphenyl) ethyl)oxazole (1.66 g, 5.88 mmol) and ethyl orthoformate (20 ml) was refluxed for 5 hr and the reaction mixture was evaporated under reduced pressure to a residue. To the residue in ethanol (50 ml) was added sodium borohydride (0.27 g, 7.14 mmol) under cooling, then the mixture was stirred at room temperature for 2 hr. After evaporation, the residue was extracted with ethyl acetate and the extracts were washed with water, dried and then evaporated under reduced pressure to a residue, which was chromatographed and recrystallized to afford 4-(1-(2-fluoro-4-biphenyl)ethyl)-2-methylaminooxazole (0.66 g, 40% yield): mp 133.5-135.0°C.

According to substantially the same procedure as that of Example 57, there was obtained the azole derivative of the formula (XXIV) as listed in Table 16.

Table 16

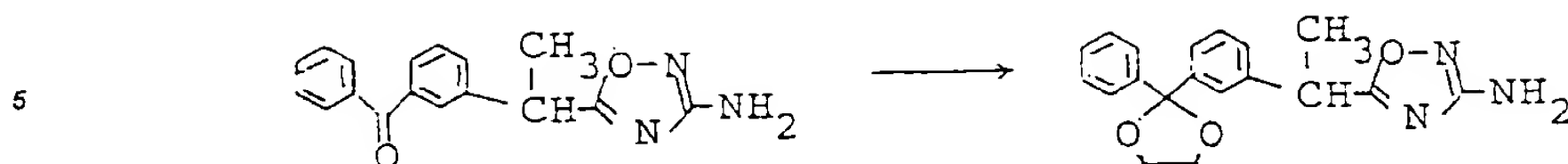
Example	Structure	Physical Data
58		mp 104.0-105.0°C

- Cont'd -

Table 16 (Cont'd)

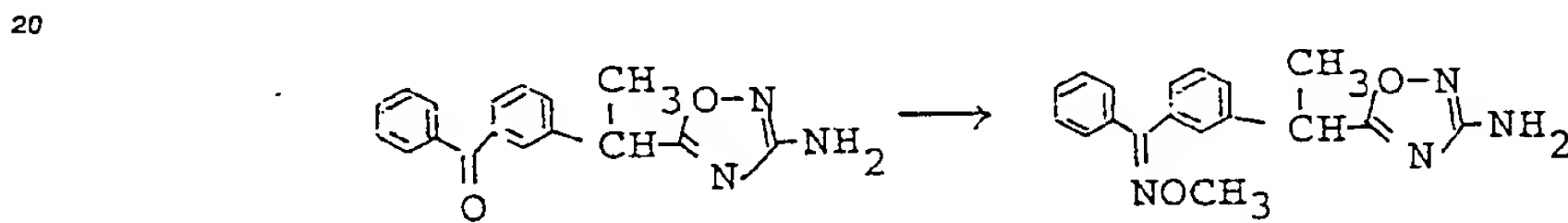
59		NMR (CDCl ₃) δ 1.59 (d, 3H), 2.85 (d, 3H), 4.04 (s, 4H), 4.05 (q, 1H), 4.34 (m, 1H), 4.63 (s, 1H), 7.15-7.60 (m, 9H) ppm; IR (neat) 3300, 2980, 1620, 1420, 1215 cm ⁻¹
60		mp 135.5-136.5°C
61		NMR (CDCl ₃) δ 1.65 (d, 3H), 2.88 (d, 3H), 4.03 (s, 4H), 4.20 (q, 1H), 4.33 (m, 1H), 7.16-7.60 (m, 9H) ppm; IR (neat) 3330, 3000, 2900, 1610, 1460, 1220, 1180, 1090, 1080 cm ⁻¹

Example 62



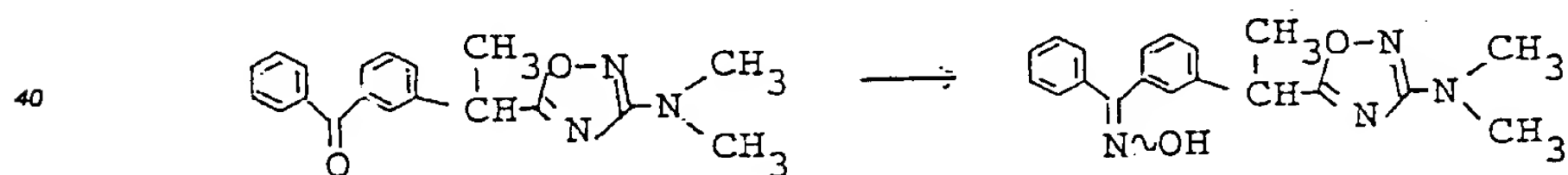
10 To 3-amino-5-(1-(3-benzoylphenyl)ethyl)-1,2,4-oxadiazole (1.20 g, 4.09 mmol) in toluene (10 ml) were added ethyleneglycol (0.80 g, 12.9 mmol) and p-toluenesulfonic acid monohydrate (0.025 g, 0.15 mmol). After reflux for 10 h, the mixture was cooled at room temperature and extracted with toluene. The extracts were washed with aqueous sodium hydrogen carbonate and then water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to a residue, which was chromatographed to afford 3-amino-5-(1-(3-(2-phenyl-1,3-dioxolan-2-yl)phenyl)ethyl)-1,2,4-oxadiazole (1.06 g, 77% yield) as crystalline material: mp 112.0-113.5°C.

Example 63



30 To 3-amino-5-(1-(3-benzoylphenyl)ethyl)-1,2,4-oxadiazole (0.60 g, 2.0 mmol) in pyridine (10 ml) was added methoxyamine hydrochloride (0.224 g, 2.7 mol). After reflux with stirring for 18 h, the mixture was poured upon ice water, extracted with ethylacetate. The extracts were washed with water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to a residue, which was chromatographed to afford 3-amino-5-(1-(3-(α-methoxyiminobenzyl)phenyl)ethyl)-1,2,4-oxadiazole (0.678 g, quantitative yield) as oily substance: NMR(CDCl₃) δ 1.70 (d, 3H), 3.97(s, 3H), 4.24(q, 1H), 4.48(broad singlet, 2H), 7.21-7.58(m, 9H) ppm; IR(neat) 3310, 3220, 1625, 1585, 1410, 1050 cm⁻¹.

Example 64



45 To 3-dimethylamino-5-(1-(3-benzoylphenyl)ethyl)-1,2,4-oxadiazole (1.0 g, 3.11 mmol) in ethanol (10 ml) were added hydroxylamine hydrochloride (0.25 g, 3.45 mmol) in water (2 ml) and sodium hydroxide (0.40 g, 9.5 mmol) in water (2 ml). After reflux with stirring for 24 h, the mixture was poured upon ice water and extracted with ethyl acetate. The ethyl acetate extracts were washed with saturated NaCl aq. dried with anhydrous magnesium sulfate, and evaporated under reduced pressure to a residue, which was chromatographed to afford 3-dimethylamino-5-(1-(3-(α-hydroxyiminobenzyl)phenyl)ethyl)-1,2,4-oxadiazole (0.873 g, 84% yield) as oily substance: NMR(CDCl₃) δ 1.66(d) + 1.77(d) (3H), 2.98(s, 6H), 4.20(m, 1H), 7.22-7.55(m, 9H) ppm; IR(neat) 3700-3100, 1600, 1405 cm⁻¹.

According to substantially the same procedure as that of Example 64, the following compounds were made.

Table 17

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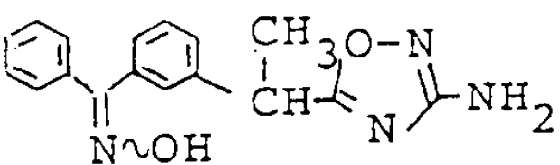
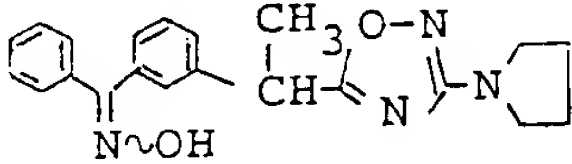
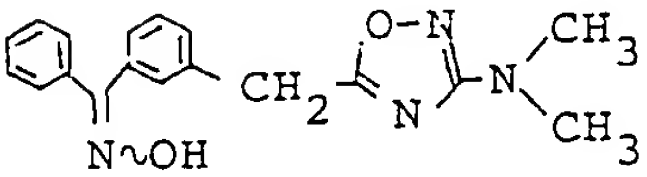
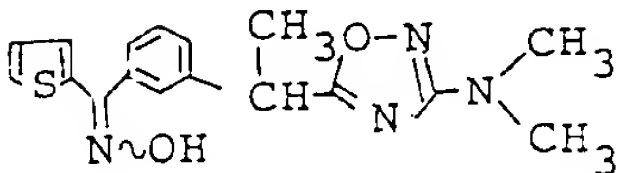
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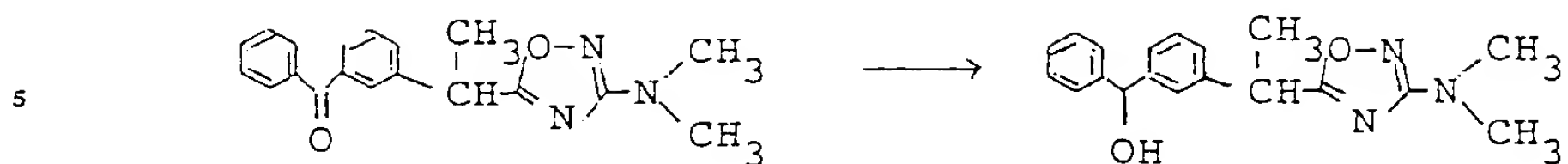
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Example No.	Structure	Physical Data
65	 <p>(mixture of syn and anti)</p>	NMR (CDCl ₃) δ 1.66 (d) + 1.69 (d) (3H), 4.12 (q) + 4.26 (q) (1H), 4.96 (br) +5.08 (br) (2H), 7.16-7.73 (m, 9H), 10.20 (br, 1H) ppm; IR (neat) 3325, 3200, 1630, 1460 cm ⁻¹
66	 <p>(mixture of syn and anti)</p>	NMR (CDCl ₃) δ 1.62 (d) + 1.72 (d) (3H), 1.80~2.03 (m, 4H), 3.23-3.53 (m, 4H), 4.26 (m, 1H), 7.17-7.53 (m, 9H), 9.62 (br, 1H) ppm; IR (neat) 3250, 1600, 1490, 1415, 1200 cm ⁻¹
- Cont'd -		
Table 17 (Cont'd)		
67	 <p>(mixture of syn and anti)</p>	NMR (CDCl ₃) δ 2.95 (s) + 2.97 (s) (6H), 4.02 (s) + 4.10 (s) (2H), 7.24~7.52 (m, 9H), 9.68 (br, 1H) ppm; IR (neat) 3250, 1600, 1400 cm ⁻¹
68	 <p>(mixture of syn and anti)</p>	mp 189.0~190.0°C

Example 69



10 To sodium brohydride suspended (0.177 g, 4.7 mmol) in methanol (15 ml) under cooling with ice was slowly added dropwise 3-dimethylamino-5-(1-(3-benzoylphenyl) ethyl)-1,2,4-oxadiazole (1.45 g, 4.5 mmol) in methanol (15 ml). After the mixture was stirred under cooling with ice for 1 h, 1N-HCl was added to the mixture, then the mixture was adjusted at pH 6. The mixture was evaporated under reduced pressure to a residue, which was extracted with dichloromethane. The extracts were washed with saturated NaCl aq., dried with anhydrous magnesium sulfate, and evaporated under reduced pressure to a residue, which was chromatographed to afford 3-dimethylamino-5-(1-(3-(α-hydroxybenzyl)phenyl)ethyl)-1,2,4-oxadiazole (1.50 g, 99% yield) as oily substance: NMR(CDCl₃) δ 1.45(d, 3H), 2.27(d, 1H), 3.00(s, 6H), 4.20(q, 1H), 5.80(d, 1H), 7.20-7.45(m, 9H) ppm; IR(neat) 3375, 1600, 1405 cm⁻¹.

20 According to substantially the same procedure as that of Example 69, the following compound was made.

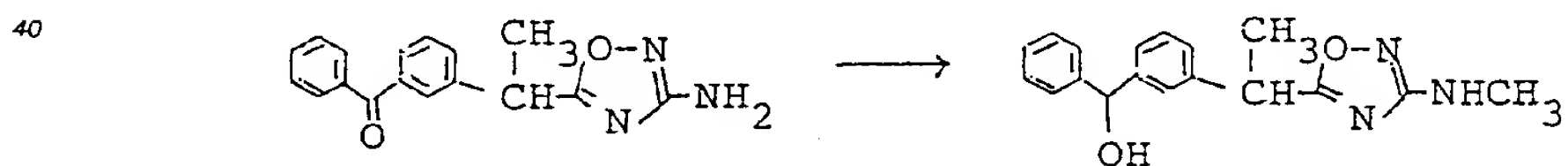
Table 18

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Example No.	Structure	Physical Data
30 70		NMR(CDCl ₃) δ 1.65 (d, 3H), 2.96 (br, 1H), 4.19 (q, 1H), 4.50 (br, 2H), 5.78 (s, 1H), 7.15~7.48 (m, 9H) ppm; IR(neat) 3500~3200, 1630, 1590, 1420 cm ⁻¹

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Example 71

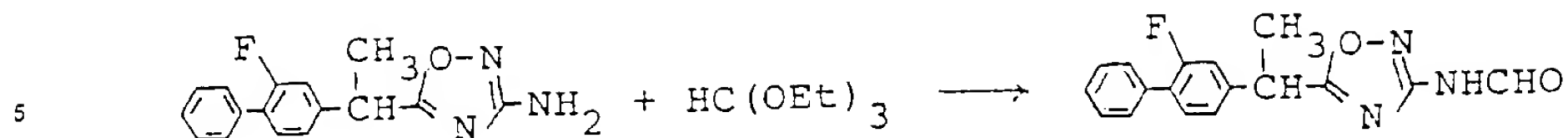


45 To triethyl orthoformate (10 ml) was added 3-amino-5-(1-(3-benzoylphenyl)ethyl)-1,2,4-oxadiazole (0.30 g, 1.02 mmol). After reflux for 4.5 h, the mixture was evaporated under reduced pressure to a residue, which was extracted with dichloromethane after saturated NaHCO₃ aq. was added. The extracts were washed with water, evaporated under reduced pressure to a residue, which was chromatographed to afford 3-methylamino-5-(1-(3-(α-hydroxybenzyl)phenyl)ethyl)-1,2,4-oxadiazole (0.15 g, 48% yield) as oily substance: NMR(CDCl₃) δ 1.63(d, 3H), 2.82(d, 4H), 4.18(q, 1H), 4.20(m, 1H), 5.73(d, 1H), 7.33-7.42(m, 9H) ppm; IR(neat) 3430, 3330, 3040, 1600, 1490, 1450, 1340, 1320, 1150 cm⁻¹.

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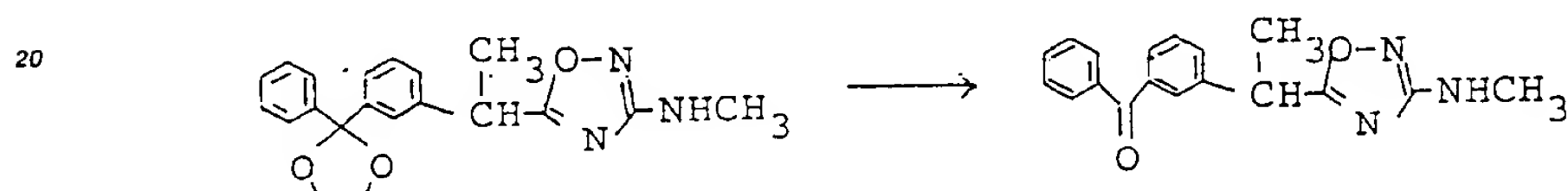
Example 72



10 To triethyl orthoformate (6 ml) was added 3-amino-5-(2-(2-fluoro-4-biphenyl)ethyl)-1,2,4-oxadiazole (0.10 g, 0.35 mmol). After the mixture was refluxed for 20 h, the mixture was evaporated under reduced pressure to a residue, which was extracted with chloroform after water was added. The extracts were dried with anhydrous potassium carbonate, and evaporated under reduced pressure to a residue, which was chromatographed to afford 3-formylamino-5-(2-(2-fluoro-4-biphenyl)ethyl)-1,2,4-oxadiazole (0.091 g, 83% yield): NMR(CDCl₃) δ 1.86(d, 3H), 4.40(q, 1H), 7.00-7.65(m, 8H), 9.06(broad, 2H) ppm; IR(nujol) 3275, 1740, 1580 cm⁻¹; mass m/e 311 (M⁺).

15

Example 73



25 To the mixture of acetic acid (16 ml) and water (4 ml) was added 3-methylamino-5-(1-(3-(2-phenyl-1,3-dioxolan-2-yl)phenyl)ethyl)-1,2,4-oxadiazole (0.643 g, 2.44 mmol). After the mixture was stirred at room temperature overnight, the mixture was evaporated under reduced pressure to a residue, which was extracted with dichloromethane after saturated NaHCO₃ aq. was added. The extracts were washed with water, dried with anhydrous magnesium sulfate, and evaporated under reduced pressure to a residue, which was chromatographed and recrystallized with ethyl acetate and n-hexane to afford 3-methylamino-5-(1-(3-benzoylphenyl)ethyl)-1,2,4-oxadiazole (0.446 g, 59% yield) as crystalline material: mp 100-101°C.

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According to substantially the same procedure as that of Example 73, the following compounds were made.

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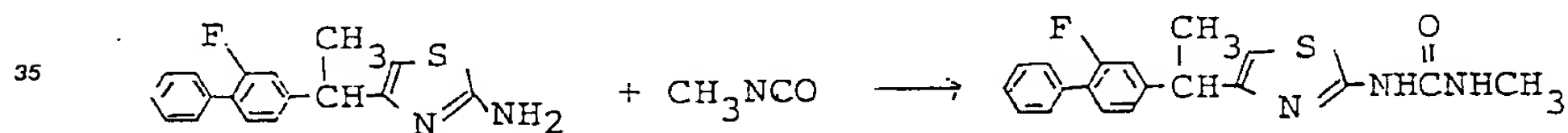
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Table 19

Example No.	Structure	Physical Data
74		NMR (CDCl ₃) δ 1.60 (d, 3H), 4.12 (q, 1H), 4.40 (m, 2H), 4.86 (s, 1H), 7.23~7.85 (m, 9H) ppm; IR (neat) 3300, 3280, 1650, 1620, 1580, 1480, 1310 cm ⁻¹
75		NMR (CDCl ₃) δ 1.63 (d, 3H), 2.83 (d, 3H), 4.13 (q, 1H), 4.36 (m, 1H), 4.70 (s, 1H), 7.23~7.88 (m, 9H) ppm; IR (neat) 3350, 2980, 1660, 1630, 1420, 1280 cm ⁻¹
76		NMR (CDCl ₃) δ 1.63 (d, 3H), 2.90 (s, 6H), 4.13 (q, 1H), 4.62 (s, 1H), 7.23~7.88 (m, 9H) ppm; IR (neat) 2950, 1660, 1620, 1435, 1280 cm ⁻¹

Example 77



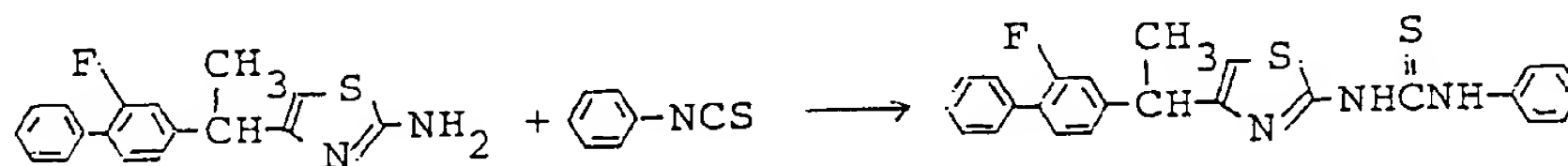
To 2-amino-4-(1-(2-fluoro-4-biphenyl)ethyl) thiazole (500 mg, 1.68 mmol) in chloroform (20 ml) was added methylisocyanate (0.10 mg, 1.75 mmol) in chloroform (10 ml) under cooling with ice. After the mixture was stirred, methylisocyanate (0.15 mmol, 2.63 mmol) was added to the mixture, and then the mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure to a residue, which was crystallized to afford N-methyl-N'-(4-(1-(2-fluoro-4-biphenyl)ethyl) thiazol-2-yl)urea (0.499 g, 84% yield) as crystalline material: mp 208.5-209.0°C.

According to substantially the same procedure as that of Example 77, the following compounds were made.

Table 20

Example No.	Structure	Physical Data
78		NMR (CDCl ₃) δ 1.65 (d, 3H), 2.87 (d, 3H), 3.39 (s, 3H), 4.13 (q, 1H), 6.48 (s, 1H), 7.04~7.56 (m, 8H), 9.32 (m, 1H) ppm; IR (neat) 3200, 1670, 1410, 1320, 1100 cm ⁻¹
79		mp 161.5~162.5°C
- Cont'd -		
Table 20 (Cont'd)		
80		mp 87.0~88.5°C
81		mp 113.0~114.0°C

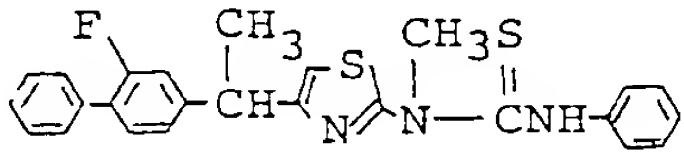
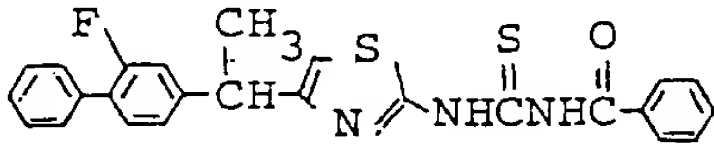
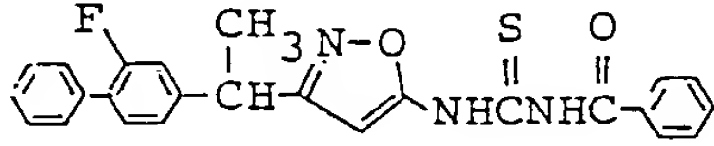
Example 82



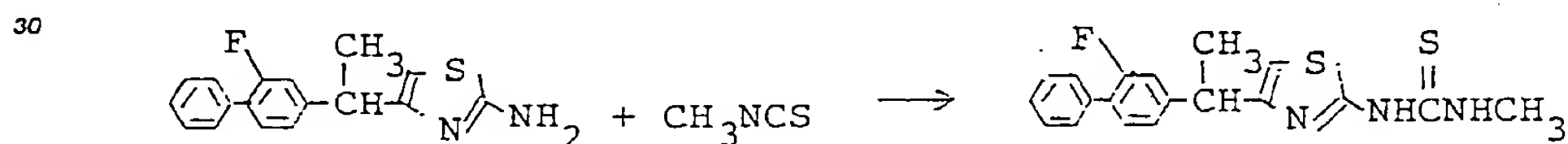
To 2-amino-4-(1-(2-fluoro-4-biphenyl)ethyl) thiazole (0.50 g, 1.68 mmol) in acetone (10 ml) were added phenylisothiocyanate (0.25 g, 1.85 mmol) in acetone (5 ml) and sodium hydrogen carbonate (0.30 g). After the mixture was refluxed for 10 h, phenylisothiocyanate (0.50 g, 3.70 mmol) was added to the mixture, and then the mixture was refluxed for 2 h. The mixture was evaporated under reduced pressure to a residue, which was chromatographed and recrystallized to afford N-phenyl-N-(4-(1-(2-fluoro-4-biphenyl)ethyl)-thiazol-2-yl)thiourea (0.115g, 16% yield) as crystalline material: mp 176.5-177.0°C.

According to substantially the same procedure as that of Example 82, the following compounds were made.

Table 21

Example No.	Structure	Physical Data
83		NMR (CDCl ₃) 1.65 (d, 3H), 3.92 (s, 3H), 4.15 (q, 1H), 6.60 (s, 1H), 6.95~7.60 (m, 13H) ppm; IR (neat) 2930, 1560, 1490, 1300, 1180, 1060 cm ⁻¹
84		mp 162.0~163.0°C
85		mp 158.0~159.0°C

Example 86



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To lithium diisopropylamide in tetrahydrofuran prepared with diisopropylamine (0.187 g, 1.85 mmol) and n-butyllithium (1.9 mmol) was added 2-amino-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (0.50 g, 1.68 mmol) in tetrahydrofuran at -70°C. After the mixture was stirred for 20 min, methylisothiocyanate (0.131 g, 1.8 mmol) in tetrahydrofuran was added to the mixture. After the mixture was stirred at room temperature for 3.5 h, the mixture was evaporated under reduced pressure to a residue, which was extracted with chloroform. The extracts were washed with water, dried over, and evaporated under reduced pressure to a residue, which was chromatographed and recrystallized to afford N-methyl-N'-(4-(1-(2-fluoro-4-biphenyl)ethyl)thiazol-2-yl)thiourea (0.233 g, 35% yield) as crystalline material: mp 180.5-181.0°C.

45 According to substantially the same procedure as that of Example 86, the following compounds were made.

50

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Table 22

Example No.	Structure	Physical Data
87		NMR (CDCl ₃) δ 1.68 (d, 3H), 3.15 (d, 3H), 3.90 (s, 3H), 4.17 (q, 1H), 6.60 (s, 1H), 6.97~7.6 (m, 8H), 11.89 (br, 1H) ppm; IR (neat) 3110, 1560, 1500, 1300, 1045 cm ⁻¹
88		NMR (CDCl ₃) δ 1.66 (d, 3H), 0.80-2.20 (m, 1H), 3.90 (s, 3H), 4.16 (q, 1H), 6.65 (s, 1H), 6.90-7.67 (m, 8H), 11.90 (m, 1H) ppm; IR (neat) 3150, 1560, 1500, 1335, 1315, 1075, 1040, 760 cm ⁻¹
89		mp 172.0-173.0°C
90		mp 167.0-178.0°C

Example 91



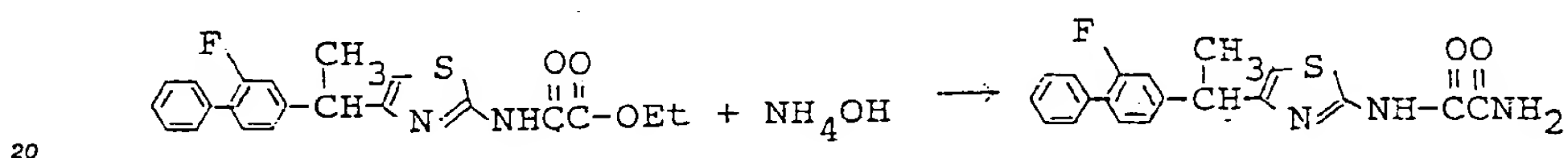
To N-benzoyl-N'-(4-(1-(2-fluoro-4-biphenyl)ethyl)thiazol-2-yl)thiourea (0.25 g, 0.561 mmol) in mixture of acetone (10 ml) and methanol (2.5 ml) was added potassium carbonate (0.05 g) in water (1 ml). After the mixture was refluxed for 5 h, the mixture was extracted with ethyl acetate. The extracts were washed with water, dried over, and evaporated under reduced pressure to residue, which was chromatographed and recrystallized with mixture of chloroform and n-hexane to afford N-(4-(1-(2-fluoro-4-biphenyl)ethyl)thiazol-2-yl)thiourea (0.172 g, 82% yield) as crystalline material: 192.0-194.0°C.

According to substantially the same procedure as that of Example 91, the following compound was made.

Table 23

Example No.	Structure	Physical Data
92		mp 150.0-151.0°C

Example 93



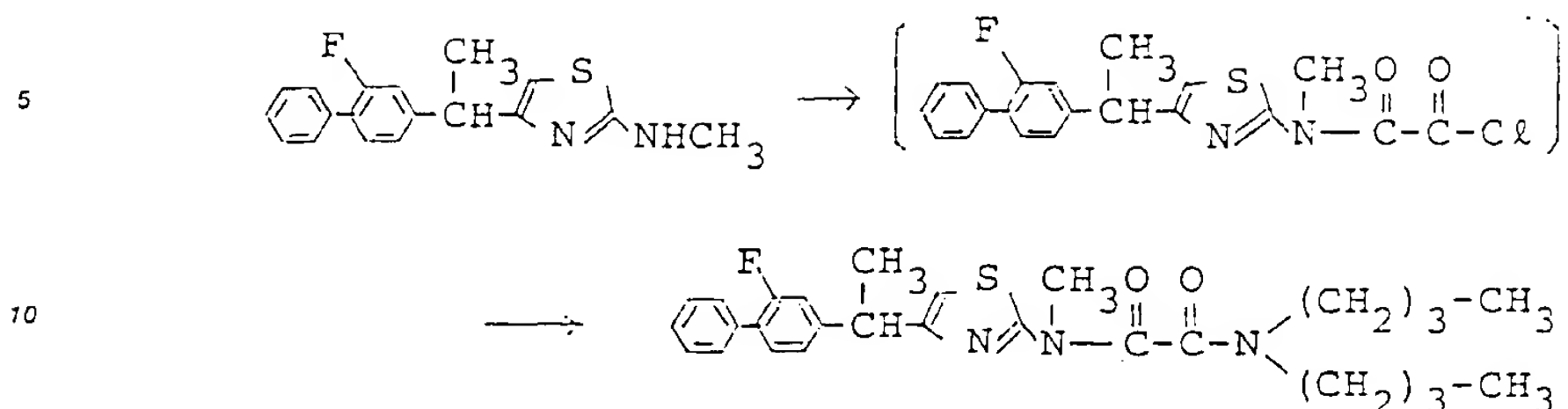
To 2-ethoxyalylamino-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (0.50 g, 1.29 mmol) in ethanol (10 ml) was added ammonia water (2 ml). After the addition, the mixture was refluxed for 2 h, evaporated under reduced pressure to a residue, which was extracted with chloroform. The extracts were dried over and evaporated under reduced pressure to residue, which was chromatographed to afford 2-oxamoylamino-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (0.121 g, 26% yield) as crystalline material: mp 179.0-180.0°C.

According to substantially the same procedure as that of Example 93, the following compound was made.

Table 24

Example No.	Structure	Physical Data
94		mp 230.5°C (decomposition)

Example 95



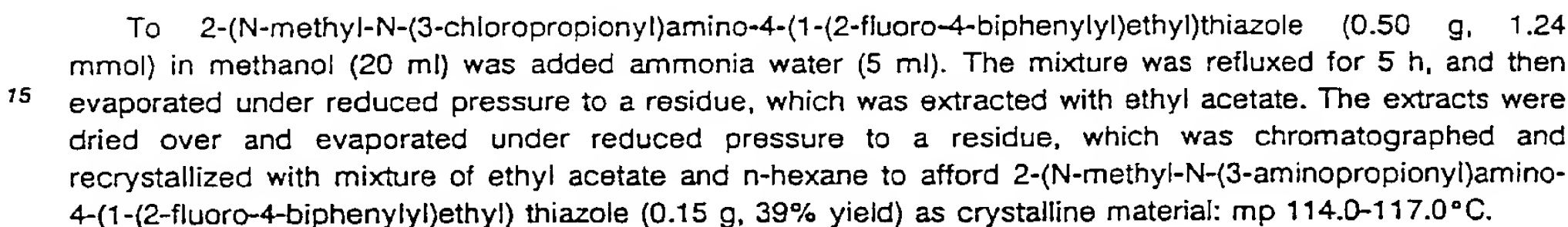
15 To oxalylchloride (1.22 g, 9.61 mmol) in tetrahydrofuran (20 ml) was added dropwise 4-(1-(2-fluoro-4-biphenyl)ethyl)-2-methylthiazole (1.00 g, 3.20 mmol) in tetrahydrofuran (10 ml). After the addition, the mixture was stirred for 1 h at room temperature, then to the mixture was added dropwise di-n-butylamine (4.14 g, 32.0 mmol) in pyridine (5 ml) under cooling. After the addition, the mixture was stirred for 1 h at room temperature and extracted with ethyl acetate. The extracts were washed with water, dried over and

20 evaporated under reduced pressure to a residue, which was chromatographed to afford N,N'-di-n-butyl-N-methyl-N-(4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole-2-yl)oxamide (142 mg, 9% yield) as oily substance: NMR(CDCl₃) δ 0.89(t, 3H), 0.97(t, 3H), 1.23-1.45(m, 4H), 1.55-1.70 (m, 9H), 3.21(t, 2H), 3.45(t, 3H), 3.63(s, 3H) 4.25(q, 1H), 6.70(s, 1H), 7.08-7.55(m, 8H)ppm; IR(neat) 2950, 1740, 1640, 1480, 1430, 1290, 1100 cm⁻¹.

25 According to substantially the same procedure as that of Example 95, the following compounds were made.

Table 25

Example No.	Structure	Physical Data
36		
40 96		mp 143.5-144.0°C
45 97		NMR(CDCl ₃) δ 1.59-1.75 (m, 9H), 3.35 (t, 2H), 3.63-3.67 (m, 5H), 4.24 (q, 1H), 6.70 (s, 1H), 7.07-7.56 (m, 8H) ppm; IR(neat) 2940, 1740, 1650, 1480, 1430, 1280, 1260, 1100 cm ⁻¹



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Chemical reaction scheme showing the synthesis of an optical isomer:

Starting materials:

- 2-(2-(2-fluorophenyl)phenyl)-2-methyl-3-(methylthio)acrylamide (Structure 1)
- 1-(4-chlorophenyl)-2-(propan-2-ylideneoxy)ethan-1-ol (Structure 2)

Reaction arrow:

Intermediate product (Structure 3):

Structure 3 is a complex molecule where the amide nitrogen of Structure 1 is linked to the propan-2-ylideneoxy group of Structure 2. The structure is shown with a chiral center marked with an asterisk (*).

Final product (Structure 4):

Structure 4 is the optical isomer of the intermediate product, shown with a chiral center marked with an asterisk (*).

(Optical Isomer)

To 4-(1-(2-fluoro-4-biphenyl)ethyl)-2-methylaminothiazole (16.0 g, 51.2 mmol) in dichloro methane (600 ml) were added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (24.0 g, 0.125 mol), N-⁴⁰hydroxybenztriazole (10.7 g, 69.9 mmol), and (+)-2-p-chlorophenyl-3-methylbutyric acid (13.5 g, 63.5 mmol) under cooling with ice. The mixture was stirred at room temperature overnight, then washed with water, dried over, and evaporated under reduced pressure to a residue, which was chromatographed to afford two diastereomers (A & B) of 2-(N-methyl-N-(2-p-chlorophenyl-3-methyl-1-oxobutyl)amino-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole as crystalline materials.

	Diastereomers	Yield	$[\alpha]_D^{25^\circ\text{C}}$ (in CHCl_3)	Chemical Purity	mp
50	A	3.73g	+52.4°	99.4%	100.5~ 101.5°C
55	B	3.99g	+31.8°	99.4%	143.0~ 143.5°C

To compound A of two diastereomers (2.50 g, 4.93 mmol) in ethanol (850 ml) was added sodium peroxide (1.92 g, 24.6 mmol). After the mixture was stirred at 50°C for 2 h, ammonia water was added to the mixture. The mixture was evaporated under reduced pressure to a residue, which was extracted with chloroform. The extracts were dried over and evaporated under reduced pressure to a residue, which was chromatographed and recrystallized to afford (+)-4-(1-(2-fluoro-4-biphenyl)ethyl)-2-methylaminothiazole (0.70 g, 45% yield) as crystalline material: mp 147.0-148.0°C; $[\alpha]_D^{25} +29.2^\circ$ (in CHCl_3); 92.6% ee*.

According to substantially the same procedure as the above without recrystallization, with compound B of two diastereomers (2.50 g, 4.93 mmol) was made (-)-4-(1-(2-fluoro-4-biphenyl)ethyl)-2-methylaminothiazole (0.90 g, 58% yield) as crystalline material: mp 143.5-145.0°C; $[\alpha]_D^{25} -21.5^\circ$ (in CHCl_3); 88.8% ee*.

*; Each of enantiomer excess (ee%) was calculated according to the following method; the diastereomers were measured by HPLC which were derived from each of optical isomers according to the same procedure as the above.

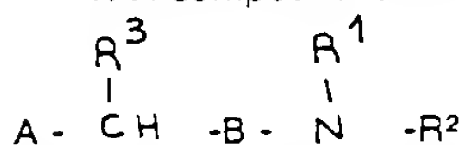
Example 100



A mixture of (+)-1-chloro-3-(2-fluoro-4-biphenyl)-2-butanone (27.7 mg, 0.1 mmol; $[\alpha]_D^{25} +180^\circ$ (c=0.744, CHCl_3), N-methylthiourea (9 mg, 0.1 mmol) and sodium bicarbonate (9.2 mg, 0.11 mmol) in methanol (1 ml) was stirred at room temperature for 28 hr and the mixture was diluted with NaCl aq., then extracted with ethyl acetate. The extracts were dried with magnesium sulfate and evaporated under reduced pressure to a residue, which was chromatographed to afford (+)-2-methylamino-4-(1-(2-fluoro-4-biphenyl)ethyl)thiazole (21.9 mg, 70% yield): $[\alpha]_D^{25} +10.7^\circ$ (c=0.15, CHCl_3); 70% ee.

Claims

1. A compound of the formula:



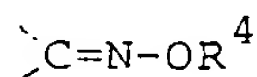
wherein A is a group of the formula:

$\text{Ar}^1 - \text{D} - \text{Ar}^2$

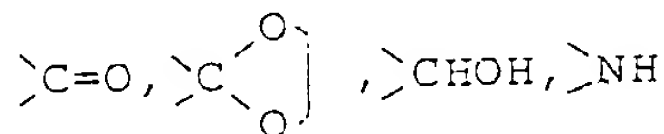
wherein Ar^1 is a phenyl or thienyl group which may be optionally substituted with at least one halogen atom;

Ar^2 is a phenylene or thienylene group which may be optionally substituted with at least one halogen atom;

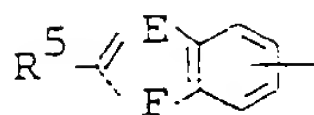
D is a divalent radical selected from the group consisting of



[wherein R^4 is a hydrogen atom or a lower alkyl group],



radical, or a single bond; a group of the formula



- 5 wherein R^5 is a lower alkoxy or a phenyl group which may be optionally substituted with at least one halogen atom; E is a methine group or a nitrogen atom; F is a vinylene group or an oxygen atom; or a group of the formula

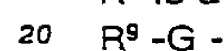


- 15 wherein R^6 is a lower alkoxy group; R^7 is a lower alkyl group; R^8 is a benzoyl group which may be optionally substituted with at least one halogen atom;

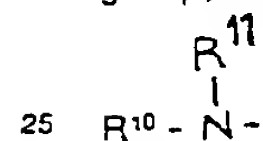
B is a divalent azole group;

R^1 is a hydrogen atom or a lower alkyl group;

R^2 is a hydrogen atom, lower alkyl, aryl-lower alkyl, or the group of the formula:



wherein R^9 is a hydrogen atom, lower alkyl, halo-lower alkyl, amino-lower alkyl, aryl or aryl-lower alkyl group; or the group of the formula:



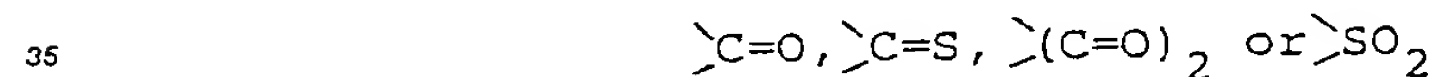
wherein R^{10} is a hydrogen atom or lower alkyl group;

R^{11} is a hydrogen atom, lower alkyl, lower alkenyl, lower cycloalkyl, aryl-lower alkyl, aryl or aroyl group; or the group of the formula: $-NR^{10}R^{11}$ is a 5-, 6- or 7-membered saturated heterocyclic ring; or the group of the formula:



wherein R^{12} is a lower alkyl or polyhalo-lower alkyl group;

G is a divalent group selected from the group consisting of



radical; or the group of the formula: $-NR^1R^2$ is a 5-, 6- or 7-membered saturated heterocyclic ring; R^3 is a hydrogen atom or a lower alkyl group, or its acid addition salts.

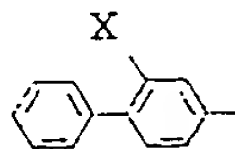
- 40 2. A compound of Claim 1 wherein B is a divalent azole group selected from thiazolediyl, oxazolediyl, isoxazolediyl or oxadiazolediyl.

3. A compound of Claim 1 wherein A is the group of the formula: Ar^1-D-Ar^2 , and B is a divalent azole group selected from thiazolediyl, oxazolediyl, isoxazolediyl or oxadiazolediyl.

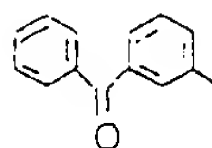
- 45 4. A compound of Claim 1 wherein A is the group of the formula: Ar^1-D-Ar^2 wherein Ar^1 is a phenyl group which may be optionally substituted with at least one halogen atom; Ar^2 is a phenylene group which may be optionally substituted with at least one halogen atom; D is a carbonyl group or a single bond; B is a divalent azole group selected from thiazolediyl, oxazolediyl, isoxazolediyl or oxadiazolediyl; and R^3 is a lower alkyl group.

5. A compound of Claim 4 wherein A is a group of the formula:

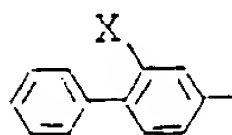
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- 55 wherein X is a hydrogen or halogen atom, or of the formula

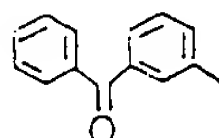


5 6. A compound of Claim 4 wherein A is a group of the formula:



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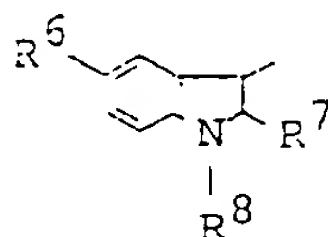
wherein X is a hydrogen or halogen atom, or of the formula:



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and R² is a hydrogen atom or a lower alkyl group.

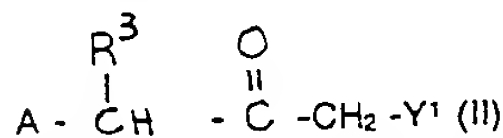
20 7. A compound of Claim 1 wherein A is the group of the formula:



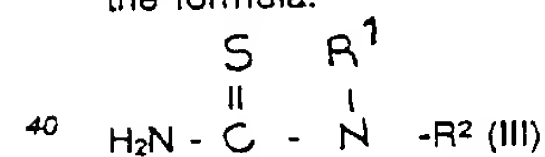
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wherein R⁶, R⁷ and R⁸ are defined in Claim 1; B is an oxadiazole-2,5-diyl group; R² is a hydrogen atom or a lower alkyl group; and R³ is a hydrogen atom.

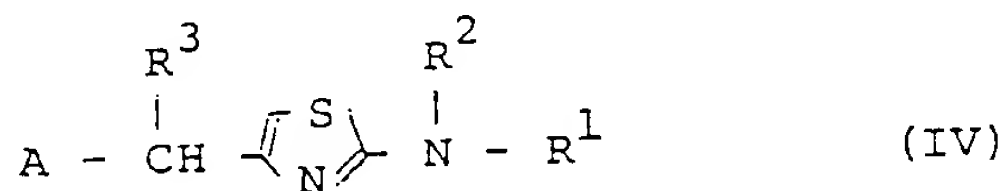
30 8. A process for preparing a compound of the formula I according to claim 1, which comprises (a) reacting an α -haloketone of the formula:



35 wherein Y¹ is a leaving group such as halogen (e.g. chlorine, bromine), alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. p-toluenesulfonyloxy), and A and R³ are as defined above, with thiourea of the formula:



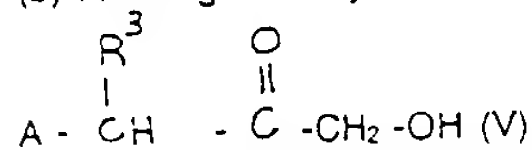
40 wherein R¹ and R² are as defined above, to yield 2-aminothiazole of the formula:



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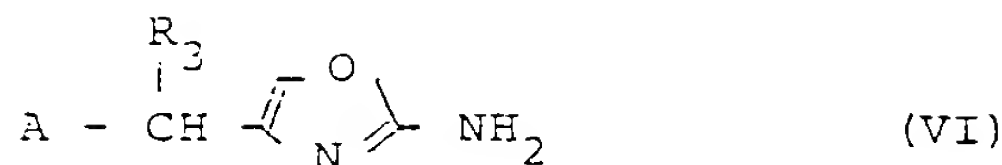
wherein A, R¹, R² and R³ are as defined above,

50 (b) reacting an α -hydroxyketone of the formula:



wherein A and R³ are as defined above, with cyanamide to yield 2-aminooxazole of the formula:

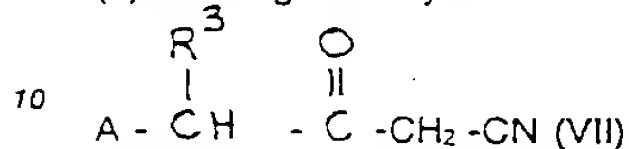
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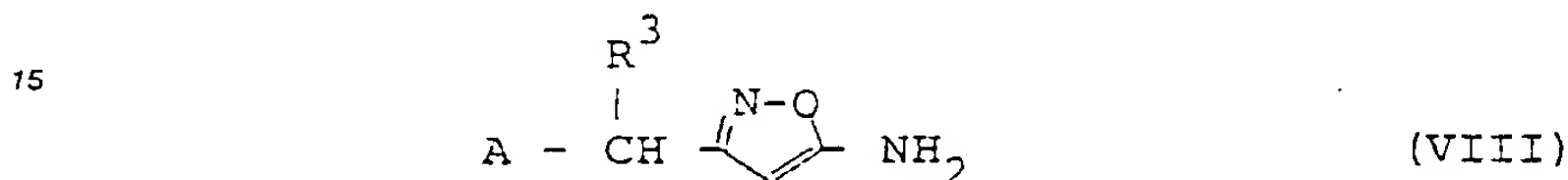
wherein A and R³ are as defined above,

(c) reacting an α-cyanoketone of the formula:



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wherein A and R³ are as defined above, with hydroxylamine to yield 5-aminoisoxazole of the formula:

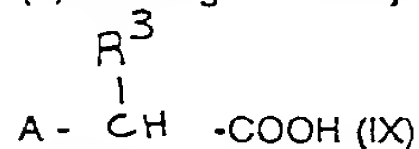


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wherein A and R³ are as defined above,

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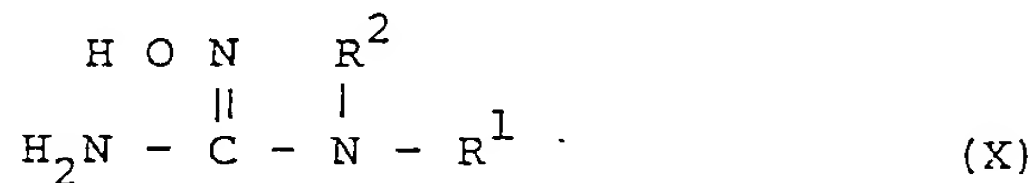
(d) reacting a carboxylic acid of the formula:



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wherein A and R³ are as defined above, or its reactive ester, with an amidoxime of the formula:

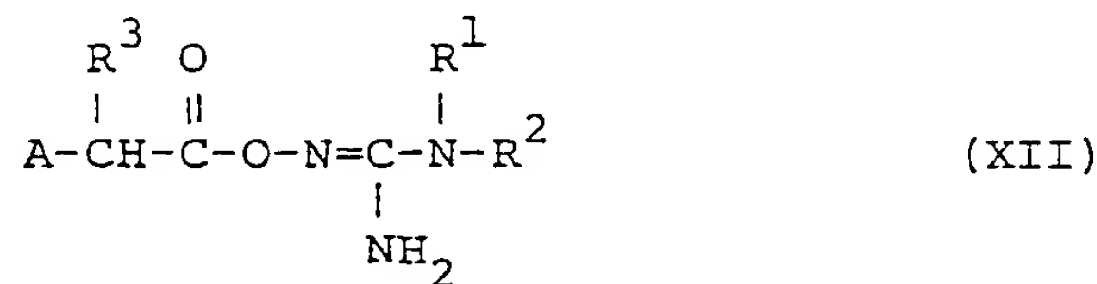
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wherein R¹ and R² are as defined above, to yield an O-acyl-amidoxime of the formula:

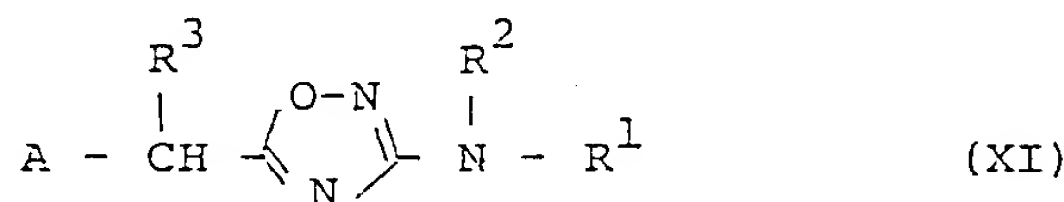
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wherein A, R¹, R² and R³ are as defined above, and further effecting intramolecular condensation to produce a compound of the formula:

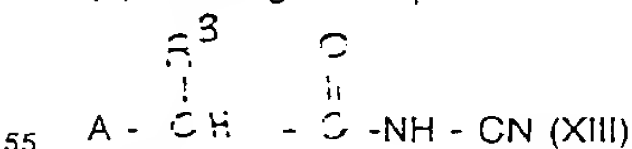
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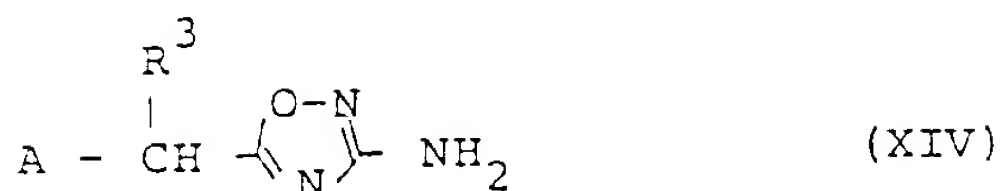
wherein A, R¹, R² and R³ are as defined above,

(e) reacting a compound of the formula:



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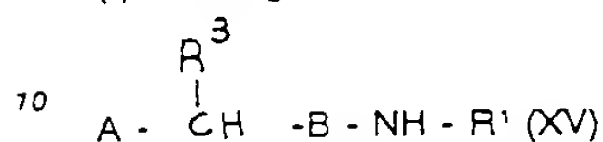
wherein A and R³ are as defined above, with hydroxylamine to yield 3-amino-1,2,4-oxadiazole of the formula:



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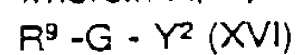
wherein A and R³ are as defined above,

(f) reacting a compound of the formula:



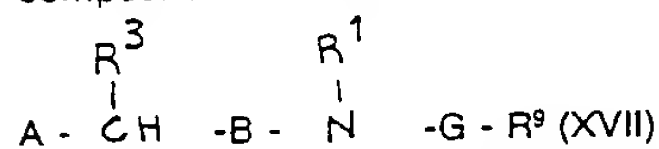
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wherein A, B, R¹ and R³ are as defined above, with a compound of the formula:



wherein Y² is a leaving group such as halogen (e.g. chlorine, bromine) alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. p-toluenesulfonyloxy), and G and R⁹ are as defined above, to yield a compound of the formula:

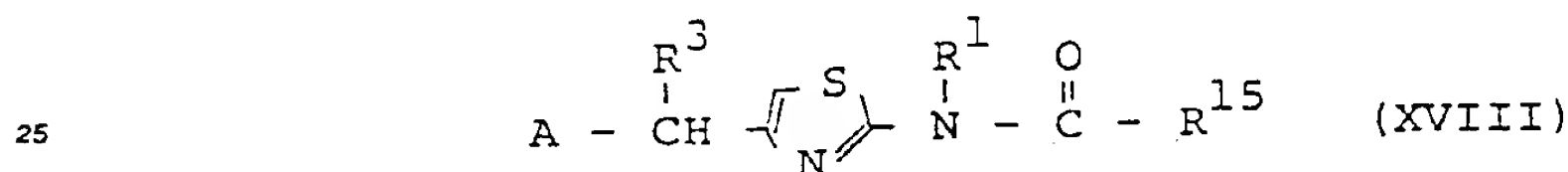
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wherein A, B, G, R¹, R³ and R⁹ are as defined above,

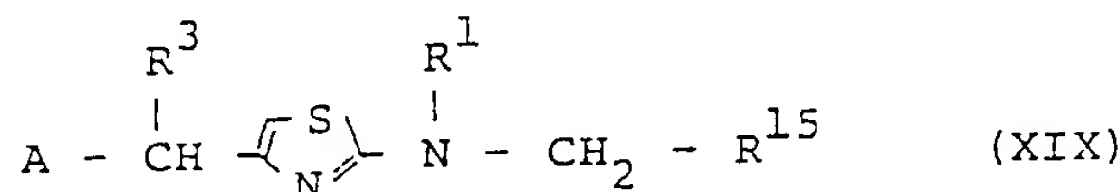
(g) reducing a compound of the formula



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wherein R¹⁵ is lower alkyl, aryl-lower alkyl or aryl, and A, R¹, R³ are as defined above, with metal hydride to yield a compound of the formula:

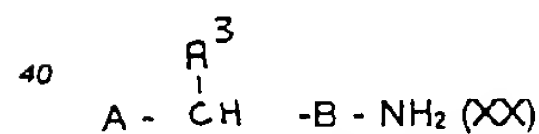
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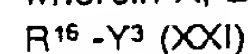
wherein A, R¹, R² and R¹⁵ are as defined above,

(h) reacting a compound of the formula:



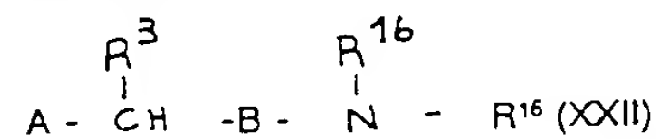
40

wherein A, B and R³ are as defined above, with a compound of the formula:



wherein Y³ is a leaving group such as halogen (e.g. chlorine, bromine), alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. p-toluenesulfonyloxy), and R¹⁶ is lower alkyl or aryl-lower alkyl, to yield a compound of the formula:

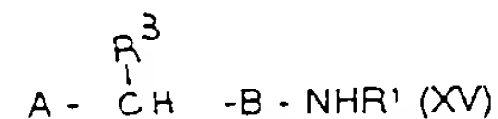
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wherein A, B, R³ and R¹⁶ are as defined above,

(i) reacting a compound of the formula:

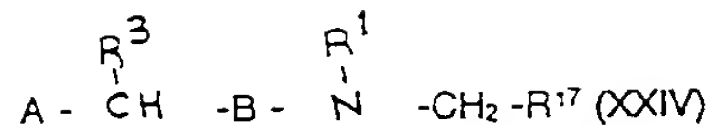


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wherein A, B, R¹ and R³ are as defined above, with a compound of the formula:

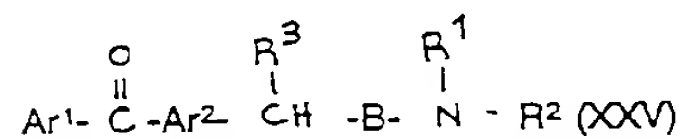


wherein R¹⁷ is hydrogen atom or lower alkyl and R¹⁸ is a lower alkyl, and then reducing with sodium borohydride to yield a compound of the formula:

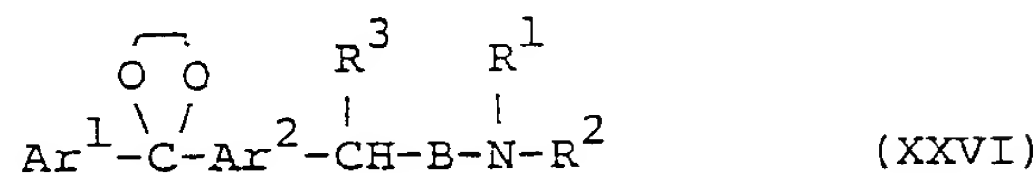


wherein A, B, R¹, R³ and R¹⁷ are as defined above,

(j) reacting a compound of the formula:

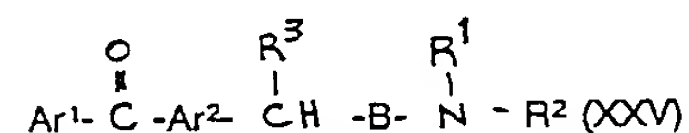


wherein Ar¹, Ar², B, R¹, R² and R³ are as defined above, with ethyleneglycol to a compound of the formula:

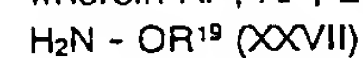


wherein Ar¹, Ar², B, R¹, R² and R³ are as defined above,

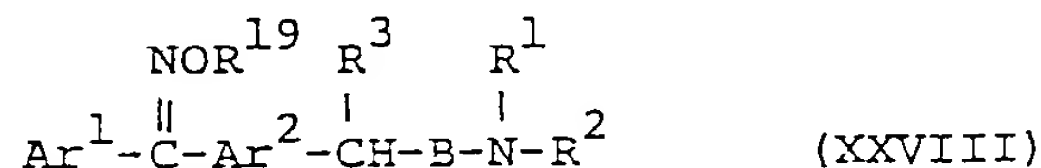
(k) reacting a compound of the formula:



wherein Ar¹, Ar², B, R¹, R² and R³ are as defined above, with a compound of the formula:

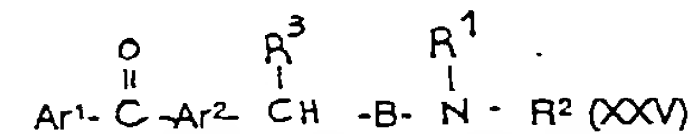


wherein R¹⁹ is hydrogen atom or lower alkyl, to yield of a compound of the formula:

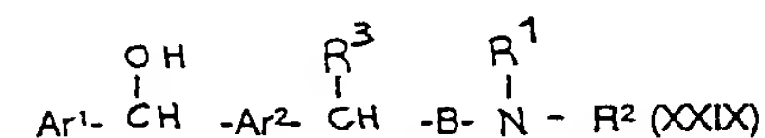


wherein Ar¹, Ar², B, R¹, R², R³ and R¹⁹ are as defined above,

(l) reducing a compound of the formula:

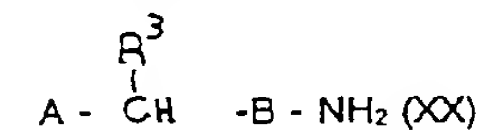


wherein Ar¹, Ar², B, R¹, R² and R³ are as defined above, with reducing agent to yield a compound of the formula:

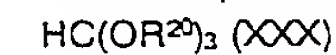


wherein Ar¹, Ar², B, R¹, R² and R³ are as defined above,

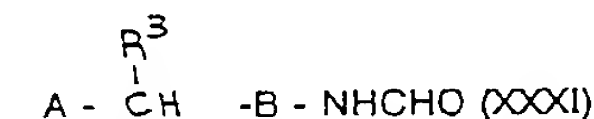
(m) reacting a compound of the formula:



wherein A, B and R³ are as defined above, with a compound of the formula:

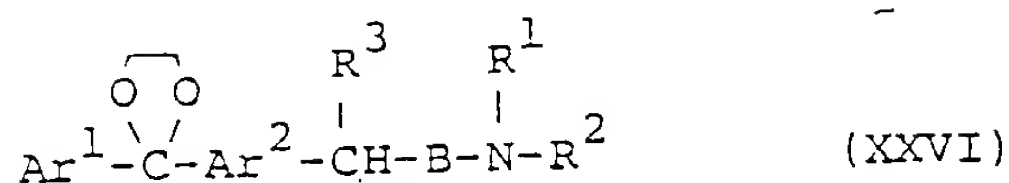


wherein R²⁰ is lower alkyl, to yield a compound of the formula:



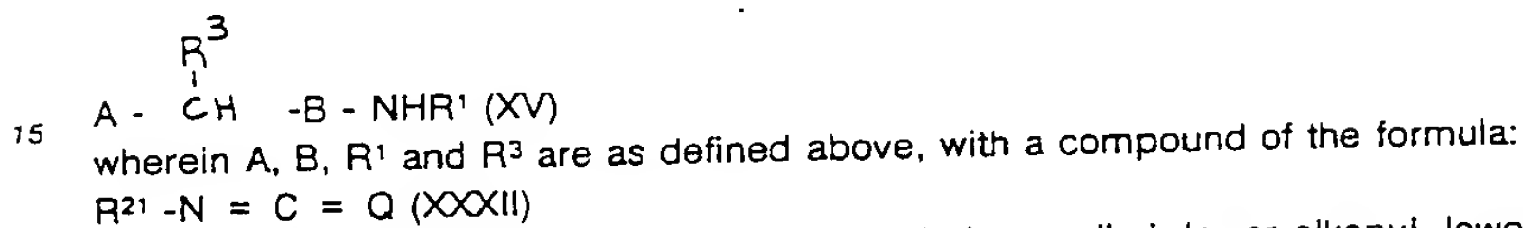
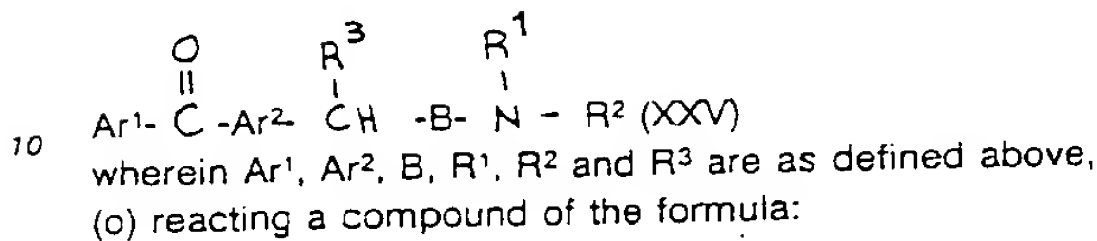
wherein A, B and R³ are as defined above,

(n) hydrolyzing a compound of the formula:

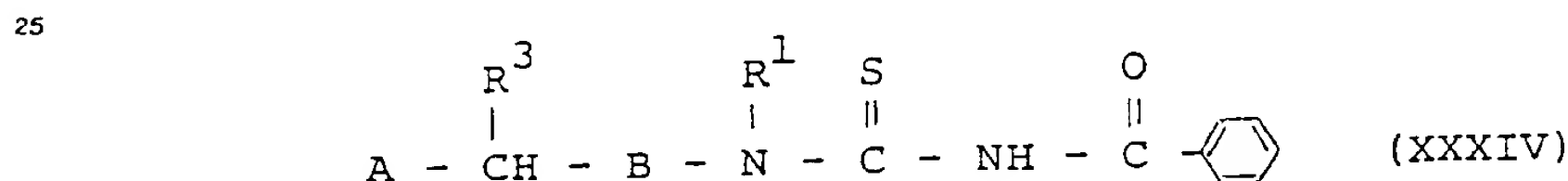
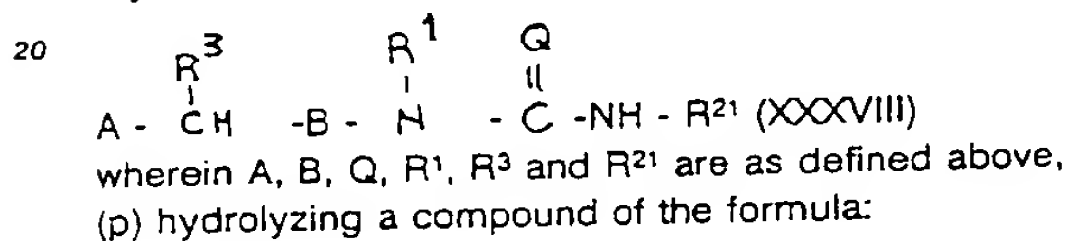


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wherein Ar¹, Ar², B, R¹, R² and R³ are as defined above, to yield a compound of the formula:

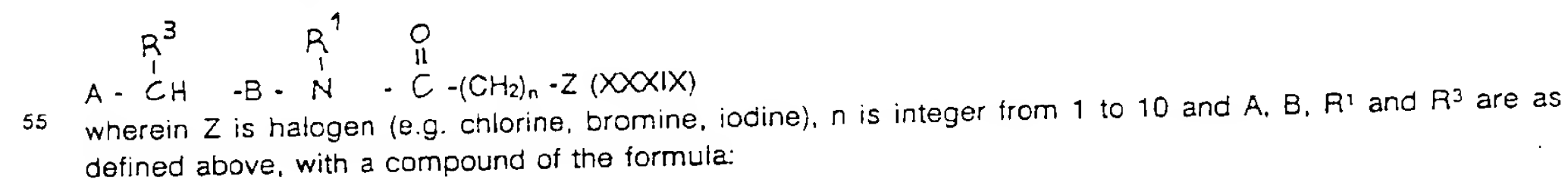
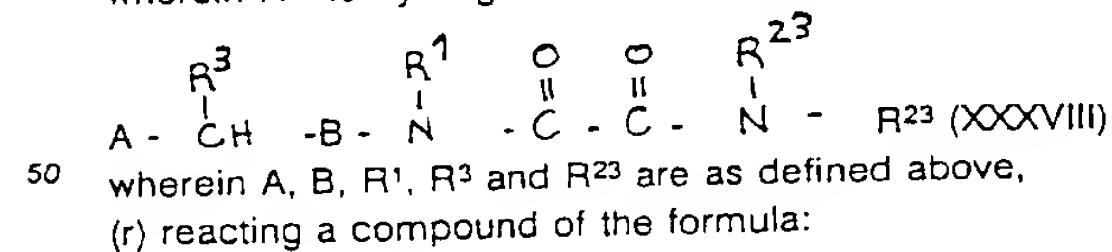
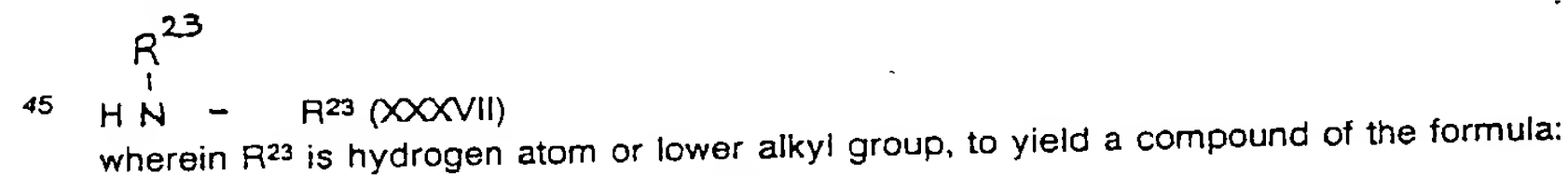
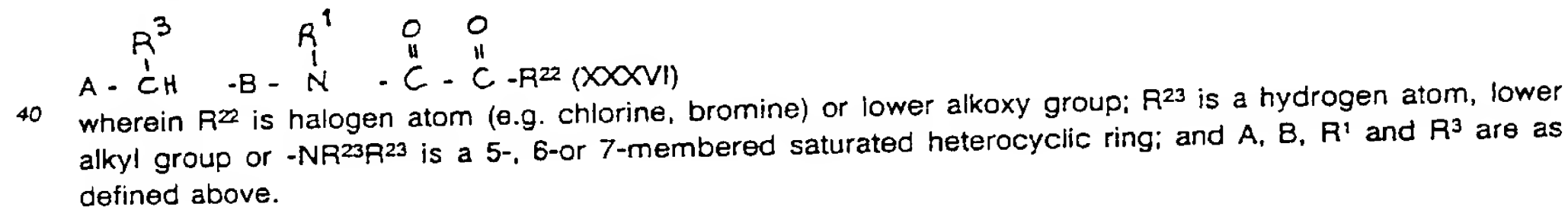
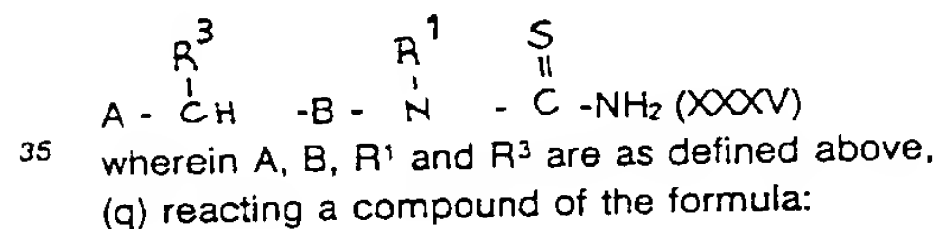


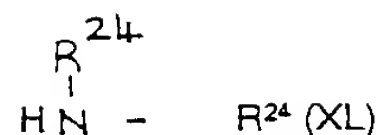
wherein Q is oxygen or sulfur atom, and R²¹ is lower alkyl, lower alkenyl, lower cycloalkyl, aryl-lower alkyl, aryl or aroyl group, to yield a compound of the formula:



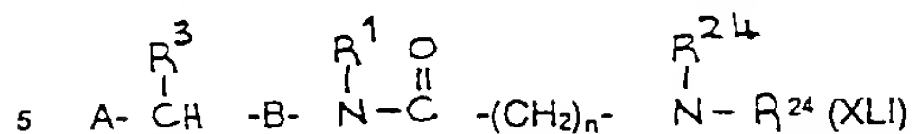
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wherein A, B, R¹ and R³ are as defined above, to yield a compound of the formula:



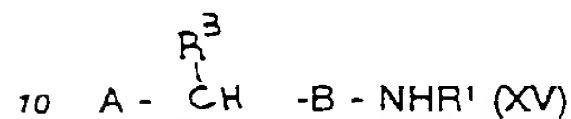


wherein R^{24} is hydrogen atom or lower alkyl group, to yield a compound of the formula:



wherein A, B, R^1 , R^3 and R^{24} are as defined above,

(s) reacting a compound of the formula:

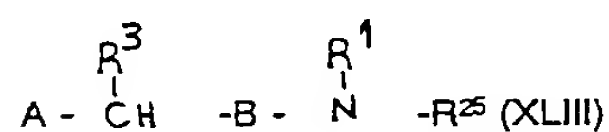


wherein A, B, R^1 and R^3 are as defined above, with a compound of the formula:



wherein Y^4 is a leaving group such as halogen (e.g. chlorine, bromine), alkylsulfonyloxy (e.g. methanesulfonyloxy) or arylsulfonyloxy (e.g. p-toluenesulfonyloxy), and $R^{\mathcal{Z}}$ is lower alkyl or aryl-lower alkyl, to yield a

15 compound of the formula:



wherein A, B, R^1 , R^3 and $R^{\mathcal{Z}}$ are as defined above.

20 9. A pharmaceutical composition for treatment of autoimmune diseases, which comprises as active ingredient a pharmaceutically effective amount of at least one compound and its pharmaceutically acceptable acid addition salts as claimed in Claim 1, and at least one pharmaceutically acceptable inert carrier or diluent.

25 10. A compound according to Claim 1 or its pharmaceutically acceptable acid addition salts for use as a therapeutic and preventive agent of autoimmune diseases.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application number

EP 87 10 7959

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 091 726 (SUMITOMO) * Claims *	1-10	C 07 D 277/38 C 07 D 261/14 C 07 D 263/48 C 07 D 271/06
A	FR-M- 5 175 (MERCK AG) * Abstract *	1,9	C 07 D 413/06 C 07 D 413/10 A 61 K 31/41
A	EP-A-0 005 091 (SCIENCE UNION) * Claims *	1,9	C 07 D 417/06 C 07 D 417/10
A	FR-A-2 100 914 (SQUIBB) * Claims; page 3 *	1,9	
A	DE-A-2 461 882 (CHINOIN GYOGYSZER) * Claims *	1,9	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 277/00 C 07 D 261/00 C 07 D 263/00 C 07 D 271/00 C 07 D 413/00 C 07 D 417/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 31-08-1987	Examiner HENRY J.C.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	